PCT/EP2004/013744

21 12 2004

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

EPO - DG 1

Signed R. Mahoney 21. 12. 2004

Dated 23 November 2004 (76)

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

1/77

THE PATENT OFFICE
J
-3 DEC 2003
LONDON

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — DES/JW/PB60602P

2. Patent application number
(The Patent Office will fill in his part) — 0328024.5

040EC03 E856925-1 D02029
P01/7700 0.00-0328024.5

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom L735870003

-3 DEC 2003

4. Title of the invention — Compounds

5. Name of your agent *(if you have one)* — Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* — 8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	60
Claim(s)	2
Abstract	
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature K Rutter Date 3-Dec-03

12. Name and daytime telephone number of person to contact in the United Kingdom: K Rutter 01279 644396

Warning

After an application for a Patent has beeen filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
b) Write your answers in capital letters using black ink or you may type them.
c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
f) For details of the fee and ways to pay please contact the Patent Office.

COMPOUNDS

This invention relates to pyrrole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, in particular their use in the treatment of conditions mediated by the action of PGE_2 at the EP_1 receptor.

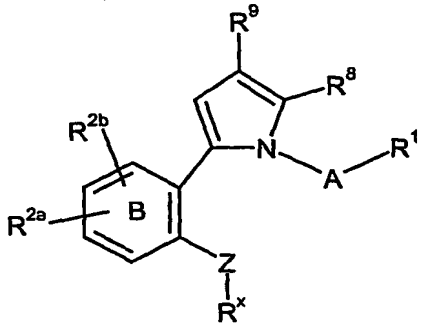
The EP_1 receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE_2. PGE_2 also has affinity for the other EP receptors (types EP_2, EP_3 and EP_4). The EP_1 receptor is associated with smooth muscle contraction, pain (in particular inflammatory, neuropathic and visceral), inflammation, allergic activities, renal regulation and gastric or enteric mucus secretion. We have now found a novel group of compounds which bind with high affinity to the EP_1 receptor.

A number of review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids; From Biotechnology to Therapeutic Applications,* Folco, Samuelsson, Maclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and Journal of Lipid Mediators and Cell Signalling, 1996, 14, 83-87 and *Prostanoid Receptors, Structure, Properties and Function,* S Narumiya et al, Physiological Reviews 1999, 79(4), 1193-126. An article from *The British Journal of Pharmacology* (1994, 112, 735- 740) suggests that Prostaglandin E_2 (PGE_2) exerts allodynia through the EP_1 receptor subtype and hyperalgesia through EP_2 and EP_3 receptors in the mouse spinal cord. Furthermore an article from *The Journal of Clinical Investigation* (2001, 107 (3), 325) shows that in the EP_1 knock-out mouse pain-sensitivity responses are reduced by approximately 50%. Two papers from *Anesthesia and Analgesia* have shown that (2001, 93, 1012-7) an EP_1 receptor antagonist (ONO-8711) reduces hyperalgesia and allodynia in a rat model of chronic constriction injury, and that (2001, 92, 233-238) the same antagonist inhibits mechanical hyperalgesia in a rodent model of post-operative pain. S. Sarkar *et al* in *Gastroenterology*, 2003, 124(1), 18-25 demonstrate the efficacy of EP_1 receptor antagonists in the treatment of visceral pain in a human model of hypersensitivity. Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, inhibit hormone-induced uterine contractions and have anti-cancer effects. These compounds have a diminished ability to induce some of the mechanism-based side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects. Moreover, by sparing potentially beneficial prostaglandin pathways, these agents may have enhanced efficacy over NSAIDS and/or COX-2 inhibitors.

In The American Physiological Society (1994, 267, R289-R-294), studies suggest that PGE_2-induced hyperthermia in the rat is mediated predominantly through the EP_1 receptor. WO 96/06822 (March 7, 1996), WO 96/11902 (April 25, 1996), EP 752421-A1 (January 08, 1997) and WO 01/19814 (22 March 2001) disclose compounds as being useful in the treatment of prostaglandin mediated diseases.

It is now surprisingly indicated that a novel group of pyrrole derivatives are selective for the EP_1 receptor over the EP_3 receptor, and are therefore potentially useful in treating conditions mediated by the action of PGE_2 at EP_1 receptors. Such conditions include inflammatory, immunological, bone, neurodegenerative and renal disorders, and pain.

Accordingly the present invention provides a compound of formula (I):



(I)

wherein:

A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

B represents a phenyl or pyridyl ring;

Z represents O, S, SO, or SO_2;

R^1 represents CO_2R^4, CN, $CONR^5R^6$, $CH_2CO_2R^4$, OR^4, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO_2alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

R^{2a} and R^{2b} independently represents hydrogen, halogen, optionally substituted alkyl, optionally substituted alkoxy, CN, SO_2alkyl, SR^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;

R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR^4, O and SO_n, wherein n is 0, 1 or 2: or R^x represents optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;

R^4 represents hydrogen or an optionally substituted alkyl;

R^5 represents hydrogen or an optionally substituted alkyl;

R^6 represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted

SO_2heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR^7;
R^7 represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;
R^8 represents hydrogen, CF_3, or C_{1-3}alkyl;
R^9 represents halogen, hydrogen, CF_3, or C_{1-3}alkyl;
Q^a and Q^b are independently selected from hydrogen and CH_3;
wherein when A is a 6-membered ring the R^1 substituent and pyrrole ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 substituent and phenyl ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;
and derivatives thereof.

Suitably A is optionally substituted phenyl, an optionally substituted 6-membered heterocyclyl ring or an optionally substituted bicyclic heterocyclyl group. More suitably A is optionally substituted phenyl, optionally substituted pyridyl or optionally substituted isoquinolinyl. When A is pyridyl, suitably the R^1 and pyrrole groups are attached to the 2- and 6-positions of the pyridine ring.

Yet more suitably A is selected from phenyl optionally substituted by methyl, pyridyl wherein the R^1 and pyrrole groups are attached to the 2- and 6-positions of the pyridine ring, and isoquinolinyl.

Optional substituents for A include up to four substituents, preferably 0 or 1 substituent, independently selected from halogen, CN, optionally substituted CO_2C_{1-6}alkyl, $CONR^5R^6$, NR^5R^6, optionally substituted NR^5COC_{1-6}alkyl, optionally substituted NR^5COphenyl, optionally substituted NR^5COpiperidinyl, optionally substituted NR^5COheterocyclyl, optionally substituted $NR^5SO_2C_{1-6}$alkyl, OH, optionally substituted OC_{1-6}alkyl, optionally substituted C_{1-6}alkyl and $NR^{10}R^{11}$ wherein R^{10} and R^{11} together with the nitrogen atom to which they are attached form a morpholine ring, a 5- or 6-membered lactam ring or a 5- or 6-membered cyclic sulphonamide, wherein R^5 and R^6 are as defined above for compounds of formula (I).

Suitable optional substituents for A include CH_3.

More suitably A is 6-methylbenzoic acid substituted on the 3-position by the pyrrolyl group, or picolinic acid substituted on the 6-position by the pyrrolyl group.

Suitably B is phenyl.

Suitably Z is O.

When R^1 is CO_2R^4, preferably R^4 is hydrogen.

Suitably R^1 is CO_2H, CH_2CO_2H, or 2H-tetrazol-5-yl-methyl. More suitably R^1 is CO_2H.

Suitably R^{2a} is hydrogen.

Suitably R^{2b} is selected from hydrogen, halogen, and optionally substituted C_{1-4}alkyl e.g. CF_3. More suitably R^{2b} is Br, Cl or CF_3.

Preferably R^{2b} is positioned 1,4- relative to the Z substituent and 1,3- relative to the phenyl ring.

Suitably R^x includes optionally substituted C_{1-8}alkyl, optionally substituted CH_2pyridyl, optionally substituted CH_2thienyl or optionally substituted CH_2phenyl. Preferably R^x represents optionally substituted CH_2phenyl.

Suitable optional substituents for R^x when CH_2phenyl include one to three substituents selected from Cl, F, Br, CH_3 and CF_3, particular substituents are selected from Cl, Br and F.

Suitably R^4 is hydrogen or C_{1-4}alkyl.

Suitably R^5 is hydrogen or C_{1-4}alkyl.

Suitably R^6 is hydrogen or C_{1-4}alkyl.

Suitably R^7 is hydrogen or C_{1-4}alkyl.

Suitably R^8 is hydrogen, CH_3 or CF_3. In one aspect R^8 is hydrogen or CF_3. In an alternative aspect R^8 is CH_3.

Suitably R^9 is hydrogen.

Suitably Q^a and Q^b are each hydrogen.

Examples of the compounds of formula (I) include:
6-{2-[5-chloro-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
3-{2-[5-chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2,4-dimethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2,6-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(3,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;

3-{2-[5-chloro-2-(2-fluoro-4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
3-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
4-{2-[5-trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid;
6-{2-[5-bromo-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-bromo-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-bromo-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-bromo-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-bromo-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-bromo-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-bromo-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(2,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;

6-{2-[5-chloro-2-(4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-chloro-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
6-{2-[5-trifluoromethyl-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid;
3-{2-[5-chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isoquinoline-1-carboxylic acid;
3-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-trifluoromethyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-trifluoromethyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-trifluoromethyl-pyrrol-1-yl}-benzoic acid;
3-{2-[5-chloro-2-(2-fluoro-benzyloxy)-phenyl]-5-trifluoromethyl-pyrrol-1-yl}-benzoic acid;
3-[2-(2-benzyloxy-phenyl)-pyrrol-1-yl]-benzoic acid;
3-[2-(5-chloro-2-benzyloxy-phenyl)-pyrrol-1-yl]-benzoic acid; and
6-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl)-pyrrol-1-yl]-picolinic acid;
and derivatives thereof.

Particular examples of compounds of formula (I) include the compounds of examples 13, 15, 17, 19, 21, 22, 24, 26, 29, 50, 51, 52, and 53 and derivatives thereof.

Preferred examples of compounds of formula (I) include the compounds of examples 24, 29, 51, and 52 and derivatives thereof.

Derivatives of the compounds of formula (I) include pharmaceutically acceptable derivatives.

The invention is described using the following definitions unless otherwise indicated.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I).

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be derivatised at more than one position.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be pharmaceutically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the

like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acid.

Preferred examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

The terms "halogen or halo" are used to represent fluorine, chlorine, bromine or iodine, more preferably fluorine, chlorine and bromine.

The term "alkyl" as a group or part of a group means a straight, branched or cyclic chain alkyl group or combinations thereof. Unless hereinbefore defined, examples of alkyl include C_{1-8}alkyl, for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopentyl or cyclohexyl or combinations thereof.

The term "alkoxy" as a group or as part of a group means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain. Unless hereinbefore defined examples of alkoxy include C_{1-8}alkoxy, for example methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, sec-butoxy, iso-butoxy, tert-butoxy, pentoxy, hexyloxy, cyclopentoxy or cyclohexyloxy.

The term "alkenyl" means linear or branched structures and combinations thereof, of the indicated number of carbon atoms, having at least one carbon-to-carbon double bond, wherein hydrogen may be replaced by an additional carbon to carbon double bond. C_{2-6}alkenyl, for example, includes ethenyl, propenyl, 1-methylethenyl, butenyl and the like.

The term "heterocyclyl" as a group or as part of a group means an aromatic or non-aromatic five or six membered ring which contains from 1 to 4 heteroatoms selected from nitrogen, oxygen or sulfur and unsubstituted or substituted by, for example, up to three substituents, preferably one or two substituents. Examples of 5- membered heterocyclyl groups include furyl, dioxalanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, triazinyl, isothiazolyl, isoxazolyl, thiophenyl, pyrazolyl or tetrazolyl. Examples of 6-membered heterocyclyl groups are pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or tetrazinyl.

The term "bicyclic heterocyclyl" when used herein means a fused bicyclic aromatic or non-aromatic bicyclic heterocyclyl ring system comprising up to four, preferably one or two, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a

carbocyclic ring. Examples of bicyclic heterocyclyl groups include quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, benzothiazolyl, benzoxadiazolyl, benzthiadiazolyl, indolyl, benztriazolyl or naphthyridinyl. Suitably the bicyclic heterocyclyl group is isoquinolinyl.

The term "aryl" as a group or as part of a group means a 5- or 6- membered aromatic ring for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic, for example naphthyl. An aryl group may be substituted by up to four, preferably one to three substituents. Preferably the aryl group is phenyl.

The term "heteroaryl" as a group or as part of a group means a monocyclic five or six membered aromatic ring, or a fused bicyclic aromatic ring system comprising two of such monocyclic five or six membered aromatic rings. These heteroaryl rings contain one or more heteroatoms selected from nitrogen, oxygen or sulfur, where N-oxides, sulfur oxides and sulfur dioxides are permissible heteroatom substitutions. A heteroaryl group may be optionally substituted by one or more substituents for example one or two substituents. Examples of "heteroaryl" used herein include furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuryl, benzothienyl, indolyl, and indazolyl.

Optional substituents for alkyl or alkenyl groups unless hereinbefore defined include OH, CO_2R^4, NR^4R^5, (O), -OC_{1-6}alkyl or halo e.g. Cl, Br or F, wherein R^4, and R^5 are as hereinbefore defined for compounds of formula (I). An alkyl or alkenyl group may be substituted by one or more optional substituents, for example up to 5, 4, 3, or 2 optional substituents. Particular substituted alkyl groups include those subsituted by one or more fluorine atoms e.g. CH_2F, CHF_2, CF_3, C_2F_5 etc, especially CF_3.

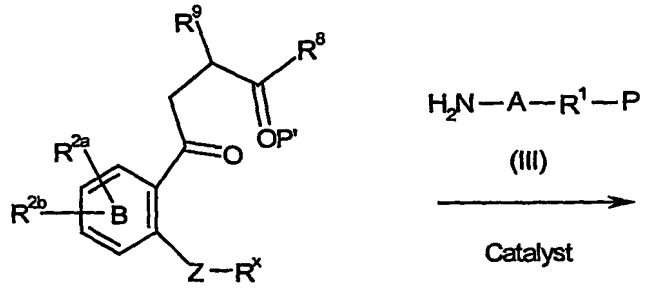
Optional substituents for alkoxy groups unless hereinbefore defined include OH, and halo e.g. Cl, Br or F. An alkoxy group may be substituted by one or more optional substituents, for example up to 5, 4, 3, or 2 optional substituents. Particular substituted alkoxy groups include those subsituted by one or more fluorines e.g. OCH_2F, $OCHF_2$, OCF_3, OC_2F_5 etc.

Optional substituents for A, aryl, heteroaryl or heterocyclyl groups, unless hereinbefore defined, include one or two substituents selected from halogen; optionally substituted C_{1-6}alkyl; optionally substituted C_{1-6}alkoxy; optionally substituted C_{2-6}alkenyl; optionally substituted C_{2-6}alkynyl; C_{1-6}haloalkyl; C_{1-6}haloalkoxy; NO_2; CN; NR^4R^5; $CONR^4R^5$; $SO_2NR^4R^5$; optionally substituted SO_nC_{1-6}alkyl; optionally substituted $NR^5(CO)C_{1-6}$alkyl; $NR^5(CO)$aryl optionally substituted by one or two substituents selected from halo, NR^4R^5, C_{1-6}alkyl, and OC_{1-6}alkyl; $NR^5(CO)$heteroaryl optionally substituted by one or two substituents selected from halo, NR^4R^5, C_{1-6}alkyl, and OC_{1-6}alkyl; and optionally substituted $NR^5(SO_2)C_{1-6}$alkyl; wherein n, R^4 and R^5 are as hereinbefore defined for compounds of formula (I).

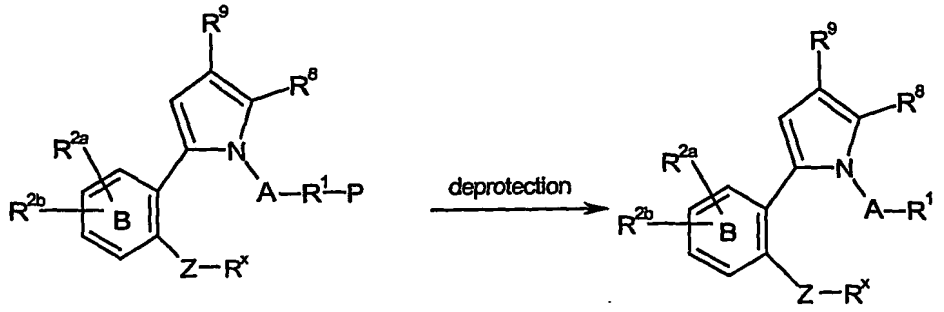
Unless otherwise defined, certain optional substituents for A, aryl, heteroaryl or heterocyclyl groups include halogen; C_{1-6}alkyl; C_{1-6}alkoxy; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{1-6}haloalkyl; C_{1-6}haloalkoxy; NO_2; CN; NR^4R^5; $CONR^4R^5$; $SO_2NR^4R^5$; SO_2C_{1-6}alkyl; $NR^5(CO)C_{1-6}$alkyl; $NR^5(CO)$phenyl; and $NR^5(CO)$heteroaryl; wherein R^4 and R^5 are as hereinbefore defined for compounds of formula (I). Alternative optional substituents include halogen, C_{1-6}alkyl, and C_{1-6}alkoxy.

When the heteroatom nitrogen replaces a carbon atom in a C_{1-8}alkyl group, or when nitrogen is present in a heteroaryl, heterocyclyl or bicyclic heterocyclyl group the nitrogen atom will, where appropriate be substituted by one or two substituents selected from hydrogen and C_{1-8}alkyl, preferably hydrogen and C_{1-6}alkyl, more preferably hydrogen.

Compounds of formula (I) can be prepared as set forth in the following scheme and in the examples. The following processes form another aspect of the present invention.



(IV)



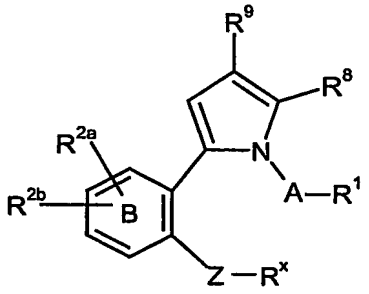
(I)

wherein P is an optional protecting group for example methyl or ethyl esters; =OP' represents an optional carbonyl protecting group; A, B, Z, R^8, R^{2a}, R^{2b}, R^1 and R^x are as defined for compounds of formula (I) and R^9 is hydrogen, C_{1-6}alkyl or CF_3. Compounds of formula (I) wherein R^9 is halogen may be prepared by treating a compound of formula (I) wherein R^9 is hydrogen with the appropriate N-halosuccinimide, for example N-chlorosuccinimide, N-bromosuccinimide or N-iodosuccinimide.

The skilled person will recognise when the use of a protecting group is necessary. When R^1 is CO_2H, a suitable protecting group P is an ester forming group such as C_{1-4}alkyl or optionally substituted benzyl. Suitable reaction conditions for the deprotection of a compound of formula (II) include hydrolysis effected by e.g. heating in ethanolic sodium hydroxide solution, or hydrogenation. Suitable carbonyl protecting groups include acetals and cyclic acetals, e.g. 1,3-dioxolane.

Suitable reaction conditions for the reaction of a compound of formula (IV) with a compound of formula (III) to give a compound of formula (II) include heating with p-toluenesulfonic acid catalyst in toluene solution.

Accordingly the present invention also provides a process for the preparation of a compound of formula (I) or a derivative thereof:



(I)

wherein:

A represents an optionally substituted aryl, or an optionally substituted 5- or 6- membered heterocyclyl ring, or an optionally substituted bicyclic heterocyclyl group;

B represents a phenyl or pyridyl ring;

Z represents O, S, SO, or SO_2;

R^1 represents CO_2R^4, CN, $CONR^5R^6$, $CH_2CO_2R^4$, OR^4, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted SO_2alkyl, $SO_2NR^5R^6$, $NR^5CONR^5R^6$, COalkyl, 2H-tetrazol-5-yl-methyl, optionally substituted bicyclic heterocycle or optionally substituted heterocyclyl;

R^{2a} and R^{2b} independently represents hydrogen, halogen, optionally substituted alkyl, optionally substituted alkoxy, CN, SO_2alkyl, SR^5, NO_2, optionally substituted aryl, $CONR^5R^6$ or optionally substituted heteroaryl;

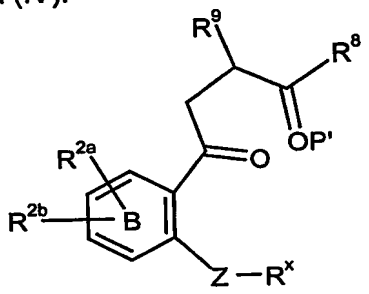
R^x represents optionally substituted alkyl wherein 1 or 2 of the non-terminal carbon atoms are optionally replaced by a group independently selected from NR^4, O and SO_n, wherein n is 0, 1 or 2: or R^x represents optionally substituted CQ^aQ^b-heterocyclyl, optionally substituted CQ^aQ^b-bicyclic heterocyclyl or optionally substituted CQ^aQ^b-aryl;

R^4 represents hydrogen or an optionally substituted alkyl;

R^5 represents hydrogen or an optionally substituted alkyl;

R^6 represents hydrogen or optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted SO_2aryl, optionally substituted SO_2alkyl, optionally substituted

SO_2heteroaryl, CN, optionally substituted CQ^aQ^baryl, optionally substituted CQ^aQ^bheteroaryl or COR^7;
R^7 represents hydrogen, optionally substituted alkyl, optionally substituted heteroaryl or optionally substituted aryl;
R^8 represents hydrogen, CF_3, or C_{1-3}alkyl;
R^9 represents halogen, hydrogen, CF_3, or C_{1-3}alkyl;
Q^a and Q^b are independently selected from hydrogen and CH_3;
wherein when A is a 6-membered ring the R^1 substituent and pyrrole ring are attached to carbon atoms 1,2-, 1,3- or 1,4- relative to each other, and when A is a five-membered ring or bicyclic heterocyclyl group the R^1 substituent and phenyl ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;
comprising:
reacting a compound of formula (IV):



(IV)

wherein P' represents an optional carbonyl protecting group, R^{2a}, R^{2b}, R^8, R^9, B, Z and R^x are as hereinbefore defined above for a compound of formula (I);
with a compound of formula (III):

$$H_2N—A—R^1—P$$

(III)

wherein A and R^1 are as hereinbefore defined above for a compound of formula (I) and P is an optional protecting group;
and where required, and in any order,
converting:
one group R^9 to another group R^9, and/or
one group R^x to another group R^x; and/or
one group R^1 to another group R^1; and/or
effecting deprotection; and/or
forming a derivative of the compound of formula (I) so formed.

It will be appreciated that certain substituents in intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art.

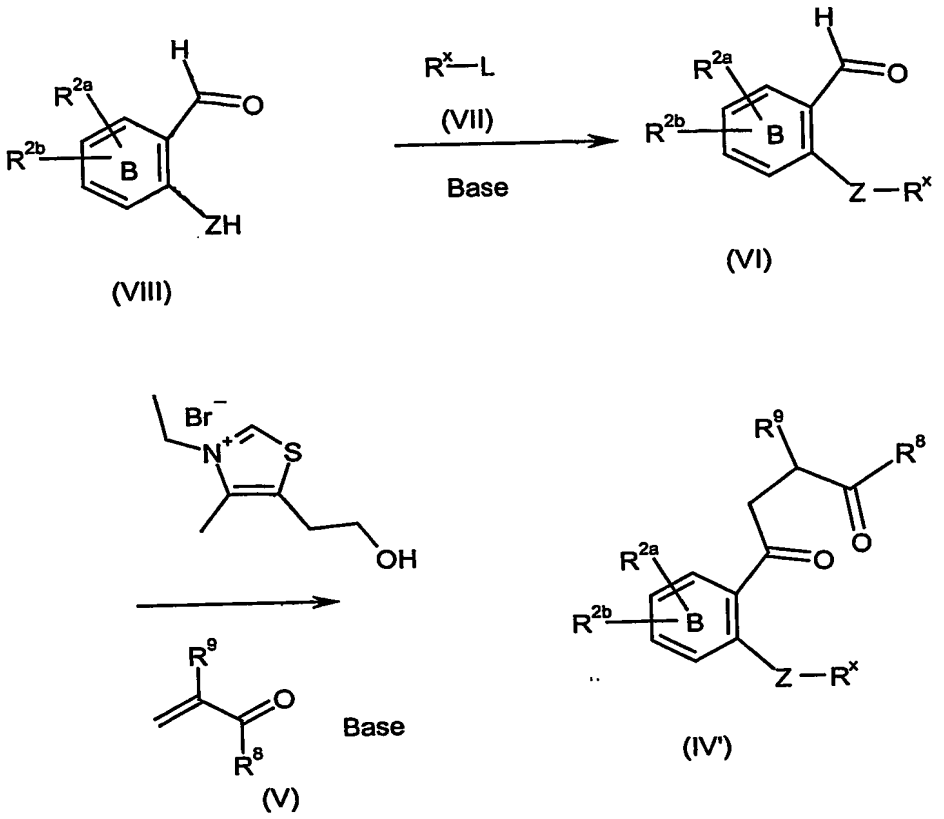
A group R^1 may be converted to another group R^1 by use of conventional organic transformations known to those skilled in the art. For example $R^1 = CO_2H$ may be converted to an amide, e.g. $CONHCQ^aQ^b$aryl or $CONHCQ^aQ^b$heteroaryl wherein Q^a and Q^b are selected from hydrogen and CH_3, by conventional methods for the preparation of amides as described in, for example, Richard Larock, *Comprehensive Organic Transformations,* 2nd edition, Wiley-VCH, ISBN 0-471-19031-4.

Certain substituents in any of the reaction intermediates and compounds of formula (I) may be converted to other substituents by conventional methods known to those skilled in the art. Examples of substituents which may be converted include one group R^x to another group R^x; and one substituent on a group A to another substituent on a group A. Examples of such transformations include the reduction of a nitro group to give an amino group; alkylation and amidation of amino groups; hydrolysis of esters, alkylation of hydroxy and amino groups; and amidation and esterification of carboxylic acids. Such transformations are well known to those skilled in the art and are described in for example, Richard Larock, *Comprehensive Organic Transformations,* 2nd edition, Wiley-VCH, ISBN 0-471-19031-4.

For example, when R^x is p-methoxybenzyl, cleavage of the ether to give the phenol or pyridinol is carried out using, for example, using acid e.g. HCl/dioxane or HBr/acetic acid or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). When R^x is methyl, cleavage of the ether to give the phenol is carried out using, for example, sodium methanethiolate. Cleavage of the ether to give a pyridinol is carried out in the presence of, for example, trifluoroacetic acid. Conversion to another R^x group, for example a substituted benzyl group, may be effected by reaction of the phenol or pyridinol with a suitable substituted benzyl bromide. The skilled person will appreciate that conversion of the protecting group P to another protecting group P may also occur under the reaction conditions used. When R^x is benzyl, cleavage of the ether to give the phenol or pyridinol may be carried out by hydrogenation according to known methods e.g. H_2-Pd/C or NH_4CO_2H-Pd/C. The resulting phenol or pyridinol can then be converted to another group R^x as described above.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. The skilled person will recognise when a protecting group is required. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, carboxylic acid groups can be protected as esters. Suitably a carbonyl group may be protected as an acetal or cyclic acetal group. Deprotection of such groups is achieved using conventional procedures known in the art. It will be appreciated that protecting groups may be interconverted by conventional means.

Compounds of formula (IV) when R^8 is other than hydrogen (compounds of formula (IV')) may be prepared via the following route:

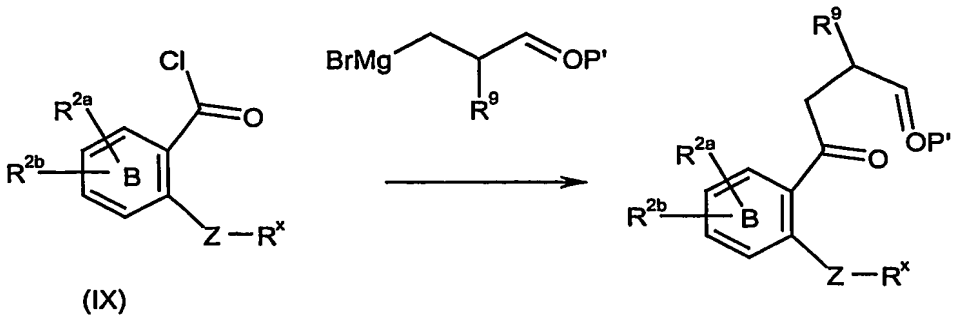


wherein L is a leaving group for example halo, e.g. bromo; B, Z, R^{2a}, R^{2b}, and R^x are as defined for compounds of formula (I), R^8 is CF_3 or C_{1-3}alkyl, and R^9 is hydrogen, C_{1-6}alkyl or CF_3.

Suitable reaction conditions for the conversion of a compound of formula (VI) to a compound of formula (IV) include heating the compound of formula (VI) with a vinyl ketone of formula (V) in the presence of a thiazolium salt e.g. 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide and an organic base, for example triethylamine, in a solvent, for example ethanol.

Suitable reaction conditions for the preparation of a compound of formula (VI) include reacting a salicylaldehyde of formula (VIII) with a compound R^x-L of formula (VII) in a solvent such as N,N-dimethylformamide, 2-butanone, acetone or tetrahydrofuran in the presence of base, e.g. potassium carbonate.

Compounds of formula (IV) when R^8 is hydrogen may be prepared for example via the following route:



(IX)

(IV)

wherein =OP' represents a protected carbonyl group, for example an acetal or cyclic acetal group e.g. a 1,3-dioxolane group; B, Z, R^{2a}, R^{2b}, and R^x are as defined for compounds of formula (I), and R^9 is hydrogen, C_{1-6}alkyl or CF_3.

Compounds of formula (III), (V), (VII), (VIII), (IX) and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide are commercially available, or readily prepared by methods known to those skilled in the art.

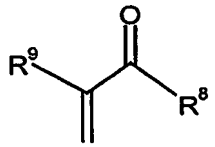
Compounds of formula (III):

$$H_2N—A—R^1—P$$

(III)

wherein P is an optional protecting group and R^1 and A are as hereinbefore defined for compounds of formula (I), are commercially available or may readily be prepared from commercially available materials according to known methods for preparing amines, e.g. using methods as described in the Examples. Methods for the preparation of amines are reviewed in *The Amino Group*, S. Patai (Ed), Interscience, New York 1968, and references cited therein. The preparation of amines is also described in Richard Larock, *Comprehensive Organic Transformations,* 2nd edition, pages 753 to 879, Wiley-VCH, ISBN 0-471-19031-4.

Intermediates of formula (V):



(V)

wherein $R^8$and R^9 are as hereinbefore defined for compounds of formula (I) are commercially available or may be readily prepared according to known methods for the preparation of vinyl ketones. For example, $F_3CCOCHCH_2$=CH_2 may be prepared according to the method of M. Tordeux *et al*, *J. Fluorine Chemistry*, 1982, 20(3), 301-306.

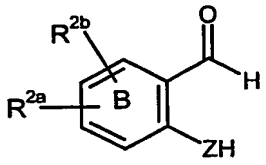
Intermediates of formula (VII):

$R^x—L$

(VII)

wherein L is as defined above and R^x is as defined for compounds of formula (I) are commercially available, or may be readily prepared by known transformations of commercially available compounds.

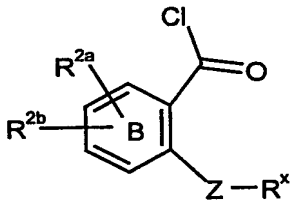
Intermediates of formula (VIII):



(VIII)

wherein R^{2a}, R^{2b}, Z and B are as defined for compounds of formula (I) are commercially available, or may readily be prepared by methods known to those skilled in the art, for example from suitable commercially available starting materials using methods as described in the examples. The preparation of aldehydes is reviewed in *The Chemistry of the Carbonyl Group*, S. Patai (Ed), Interscience, New York, 1966, and references cited therein.

Intermedates of formula (IX):



(IX)

wherein R^{2a}, R^{2b}, Z and B are as defined for compounds of formula (I) are commercially available, or may readily be prepared by methods known to those skilled in the art, for example from suitable commercially available starting materials using methods as described in the examples. The preparation of acid chlorides is reviewed in *The Chemistry of the Carbonyl Group*, S. Patai (Ed), Interscience, New York, 1966, and references cited therein.

It is to be understood that the present invention encompasses all isomers of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoismers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer

may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The compounds of the invention bind to the EP_1 receptor and they are therefore considered to be useful in treating conditions mediated by the action of PGE_2 at EP_1 receptors.

Conditions mediated by the action of PGE_2 at EP_1 receptors include pain; fever; inflammation; immunological diseases; abnormal platelet function diseases; impotence or erectile dysfunction; bone disease; hemodynamic side effects of non-steroidal anti-inflammatory drugs; cardiovascular diseases; neurodegenerative diseases and neurodegeneration; neurodegeneration following trauma; tinnitus; dependence on a dependence-inducing agent; complications of Type I diabetes; and kidney dysfunction.

The compounds of formula (I) are considered to be useful as analgesics. They are therefore considered useful in the treatment or prevention of pain.

The compounds of formula (I) are considered useful as analgesics to treat acute pain, chronic pain, neuropatic pain, inflammatory pain, visceral pain, pain associated with cancer and fibromyalgia, pain associated with migraine, tension headache and cluster headaches, and pain associated with functional bowel disorders, non-cardiac chest pain and non-ulcer dispepsia.

The compounds of formula (I) are considered useful in the treatment of chronic articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

The compounds of the invention are considered to be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and

pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) are also considered useful in the treatment of fever.

The compounds of formula (I) are also considered useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) are also considered useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) are also effective in increasing the latency of HIV infection.

The compounds of formula (I) are also considered useful in the treatment of diseases relating to abnormal platelet function (e.g. occlusive vascular diseases).

The compounds of formula (I) are also considered useful for the preparation of a drug with diuretic action.

The compounds of formula (I) are also considered useful in the treatment of impotence or erectile dysfunction.

The compounds of formula (I) are also considered useful in the treatment of bone disease characterised by abnormal bone metabolism or resorbtion such as osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cacchexia, calculosis, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendinitis and bursitis.

The compounds of formula (I) are also considered useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

The compounds of formula (I) are also considered useful in the treatment of cardiovascular diseases such as hypertension or myocardiac ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).

The compounds of formula (I) are also considered useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, ALS, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

The compounds of formula (I) are also considered useful in the treatment of neuroprotection and in the treatment of neurodegeneration following trauma such as stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

The compounds of formula (I) are also considered useful in the treatment of tinnitus.

The compounds of formula (I) are also considered useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

The compounds of formula (I) are also considered useful in the treatment of complications of Type 1 diabetes (e.g. diabetic microangiopathy, diabetic retinopathy, diabetic

nephropathy, macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

The compounds of formula (I) are also considered useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

The compounds of formula (I) are also useful in the treatment of overactive bladder and urge incontenance.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE_2 at EP_1 receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by the action of PGE_2 at EP_1 receptors.

According to another aspect of the invention we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment or prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or renal disorder.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The EP_1 receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib,

rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; EP_4 receptor ligands; EP_2 receptor ligands; EP_3 receptor ligands; EP_4 antagonists; EP_2 antagonists and EP_3 antagonists; cannabanoid receptor ligands; bradykinin receptor ligands and vanilloid receptor ligand. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

Additional COX-2 inhibitors are disclosed in US 5,474,995 US 5,633,272; US 5,466,823, US 6,310,099 and US 6,291,523; and in WO 96/25405, WO 97/38986, WO 98/03484, WO 97/14691, WO 99/12930, WO 00/26216, WO 00/52008, WO 00/38311, WO 01/58881 and WO 02/18374.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable derivatives for the treatment of man is from 0.01 to 30 mg/kg body weight per day and more particularly 0.1 to 10 mg/kg body weight per day, calculated as the free base, which may be administered as a single or divided dose, for example one to four times per day. The dose range for adult human beings is generally from 8 to 2000 mg/day, such as from 20 to 1000 mg/day, preferably 35 to 200 mg/day, calculated as the free base.

The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, and the route of administration.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following non-limiting Examples illustrate the preparation of pharmacologically active compounds of the invention.

EXAMPLES

Abbreviations:
Bn (benzyl), Bu, Pr, Me, Et (butyl, propyl, methyl ethyl), DMSO (dimethyl sulfoxide), DCM (dichloromethane), DME (ethylene glycol dimethyl ether), DMF (N,N-dimethylformamide), EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), EtOAc (ethyl acetate), EtOH (ethanol), HPLC (High pressure liquid chromatography), LCMS (Liquid chromatography/Mass spectroscopy), MDAP (Mass Directed Purification), MeOH (methanol), NMR (Nuclear Magnetic Resonance (spectrum)), NMP (n-methyl pyrrolidone), Ph (phenyl), pTSA (para-toluene sulphonic acid), SPE (Solid Phase Extraction), TBAF (tetrabutylammonium fluoride), THF (tetrahydrofuran), s, d, t, q, m, br (singlet, doublet, triplet, quartet, multiplet, broad.)

LCMS

- Column: 3.3cm x 4.6mm ID, 3um ABZ+PLUS
- Flow Rate: 3ml/min
- Injection Volume: 5μl
- Temp: RT
- UV Detection Range: 215 to 330nm
-

Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.
B: 95% Acetonitrile + 0.05% Formic Acid

Gradient: Time	A%	B%

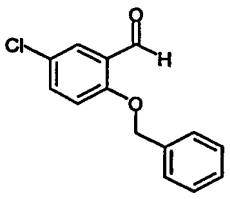
0.00	100	0
0.70	100	0
4.20	0	100
5.30	0	100
5.50	100	0

Mass Directed Autopreparation

Hardware:
Waters 600 gradient pump
Waters 2767 inject/collector
Waters Reagent Manager
Micromass ZMD mass spectrometer
Gilson Aspec - waste collector
Gilson 115 post-fraction UV detector
Software :
Micromass Masslynx version 4.0
Column
The column used is typically a Supelco LCABZ++ column whose dimensions are 20mm internal diameter by 100mm in length. The stationary phase particle size is 5μm.
Solvents:
A:. Aqueous solvent = Water + 0.1% Formic Acid
B: Organic solvent = MeCN: Water 95:5 +0.05% Formic Acid
Make up solvent = MeOH: Water 80:20 +50mMol Ammonium Acetate
Needle rinse solvent = MeOH: Water: DMSO 80:10:10

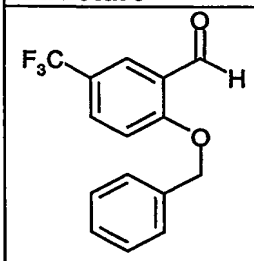
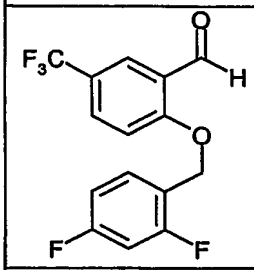
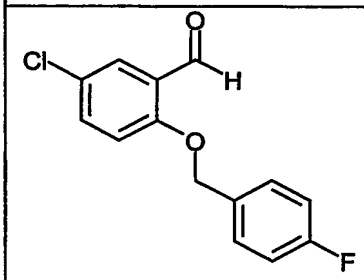
The method used depends on the analytical retention time of the compound of interest. 15-minute runtime, which comprises a 10-minute gradient followed by a 5-minute column flush and re-equilibration step.
MDP 1.5-2.2 = 0-30%B
MDP 2.0-2.8 = 5-30% B
MDP 2.5-3.0 = 15-55%B
MDP 2.8-4.0 = 30-80% B
MDP 3.8-5.5 = 50-90% B
Flow rate:
flow rate 20ml/min.

2-Benzyloxy-5-chloro-benzaldehyde

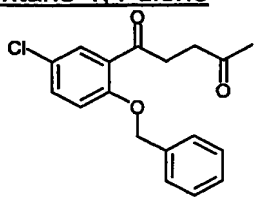


5-Chlorosalicylaldehyde (10.1g, 64.6mmol), benzyl bromide (11.5ml, 96.7mmol) and K_2CO_3 (17.9g, 13.0mmol) were heated in DMF (65ml) at 60°C for 18hrs. Upon cooling to room temperature, Et_2O and H_2O were added. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the title compound (15.8g, 100%).
^{1}H NMR (400MHz, $CDCl_3$) 5.18 (2H, s), 7.00 (1H, d, J=9Hz), 7.32-7.44 (5H, m's excess), 7.47 (1H, dd, J=3Hz, J=9Hz), 7.80 (1H, d, J=3Hz), 10.50 (1H, s).

The following compounds were prepared by a similar route to 2-benzyloxy-5-chloro-benzaldehyde from the appropriate intermediates

Structure	Name	Data
	2-Benzyloxy-5-trifluoromethyl-benzaldehyde	^{1}H-NMR (400MHz, $CDCl_3$) 5.27 (2H, s), 7.15 (1H, d, J=9Hz), 7.32-7.48 (5H, m), 7.78 (1H, dd, J=3Hz, 9Hz) 8.12 (1H, d, J=3Hz) 10.60 (1H, s). LCMS t = 3.59 min
	2-(2,4-Difluoro-benzyloxy)-5-trifluoromethyl-benzaldehyde	LCMS t = 3.74
	5-Chloro-2-(4-fluoro-benzyloxy)-benzaldehyde	LCMS t = 3.56 [MNH_4^+] 282

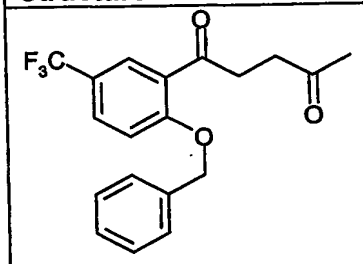
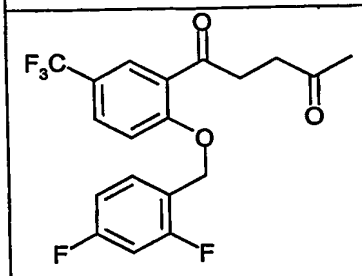
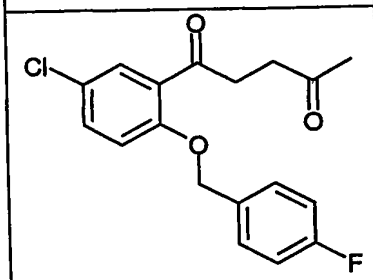
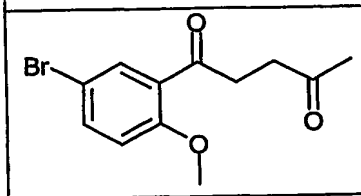
1-(2-Benzyloxy-5-chloro-phenyl)-pentane-1,4-dione



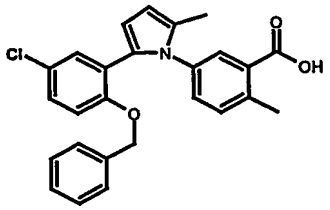
A mixture of 2-benzyloxy-5-chloro-benzaldehyde (4.04g, 16.41mmol), methyl vinyl ketone (1.64ml, 19.7mmol), 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (654mg,

2.60mmol, 0.15eq) and triethylamine (3.4ml, 28.7mmol) were heated in ethanol (5.5ml, 3M) at 80°C for 5 hours. Upon cooling, the mixture was diluted with EtOAc and washed with saturated NH_4Cl and saturated $NaHCO_3$, dried (Na_2SO_4) filtered and concentrated. The residue was purified by chromatography using Biotage with *iso*-hexane containing a gradient of EtOAc (5-15%) to give the title compound as an oil (4.01g, 81%).
^{1}H NMR (400MHz, $CDCl_3$) 2.18 (3H, s), 2.78 (2H, d, J=6Hz), 3.23 (2H, d, J=6Hz), 5.15 (2H, s), 6.95 (1H, d, J=9Hz), 7.23-7.50 (6H, m's excess), 7.70 (1H, d, J=3Hz).

The following compounds were prepared by a similar route to 1-(2-benzyloxy-5-chloro-phenyl)-pentane-1,4-dione from the appropriate intermediates

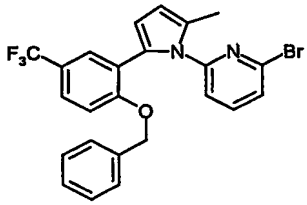
Structure	Name	Data
	1-[5-Trifluoromethyl-2-(benzyloxy)-phenyl]-pentane-1,4-dione	^{1}H-NMR (400MHz, $CDCl_3$) 2.19 (3H, s), 2.80 (2H, t, J=6Hz), 3.26 (2H, t, J=6Hz), 5.23 (2H, s), 7.10 (1H, d, J=9Hz), 7.35-7.46 (5H, m), 7.68 (1H, dd, J=3Hz, 9Hz), 8.02 (1H, d, J=3Hz). LCMS t = 3.51 min
	1-[5-Trifluoromethyl-2-(2,4-difluorobenzyloxy)-phenyl]-pentane-1,4-dione	LCMS t = 3.62 [MH-] 387
	1-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-pentane-1,4-dione	LCMS t = 3.46
	1-(5-Bromo-2-methoxy-phenyl)-pentane-1,4-dione	LCMS t = 2.84 min [MH^+] 285/287

3-[2-(5-Chloro-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-6-methyl-benzoic acid methyl ester



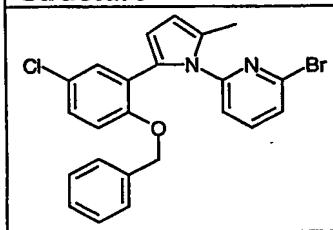
1-[5-Chloro-2-benzyloxy-phenyl]-pentane-1,4-dione (111mg), 5-amino-2-methyl-benzoic acid (61mg) and pTSA (cat) were heated in NMP (4.5mL) at 150°C for 10 minutes. The mixture was diluted with Et_2O washed with 2M HCl, dried (Na_2SO_4), filtered and evaporated. The residue was purified by MDAP, to give the title compound (89mg). LCMS t = 4.04 min, [MH^+] 432/434

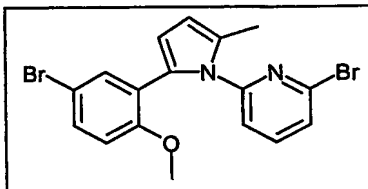
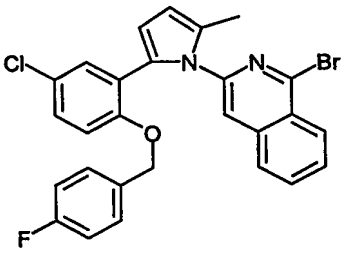
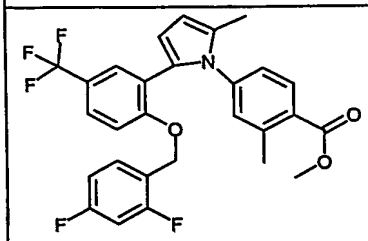
6-[2-(5-Trifluoromethyl-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-2-bromo-pyridine



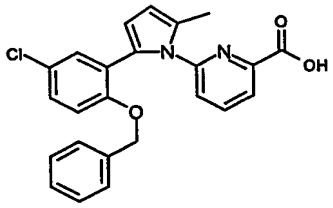
1-(2-Benzyloxy-5-trifluoromethyl-phenyl)-pentane-1,4-dione (1.5g, 4.3mmol), 2-amino-6-bromopyridine (0.75g, 4.3mmol) and *p*-TSA (10mg, cat.) in CH_3CN (5ml) were heated in a sealed vessel at 200°C for 1.5 hours using microwaves. Upon cooling the reaction was concentrated and the residue was purified by chromatography using Biotage□ with *iso*hexane / EtOAc (5%) as eluant, to give the title compound (645mg, 31%). LCMS t = 4.14 [MH^+] 487/489.

The following compounds were prepared by a similar route to 6-[2-(5-trifluoromethyl-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-2-bromo-pyridine from the appropriate intermediates

Structure	Name	LCMS
	6-[2-(5-Chloro-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-2-bromo-pyridine	t = 4.08 [MH^+] 453/455

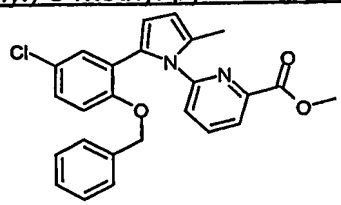
	6-{2-[5-Bromo-2-methoxy-phenyl]-5-methyl-pyrrol-1-yl}-2-bromo-pyridine	t = 3.93 [MH$^+$] 421/423/425
	1-Bromo-3-{2-[5-chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isoquinoline	t = 4.39 [MH$^+$] 521/523/525
	4-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 3.78 [MH$^+$] 512

Eaxmple 1: 6-{2-[5-Chloro-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid



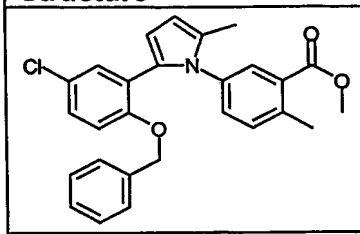
n-Butyl lithium (1.6M in hexanes, 1.44mL, 2.31mmol) was added to 6-[2-(5-chloro-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-2-bromo-pyridine (700mg, 1.54mmol) in THF (20ml) at -78°C. After 1 hour at this temperature, solid CO_2 was added and the solution warmed to room temperature. The reaction mixture was evaporated to dryness, and the resulting yellow oil was triturated with 10% EtOAc/cyclohexane. The mixture was filtered and the residue collected. The filtrate was shown to contain some product, by LCMS, so it was evaporated to dryness, and triturated with 5% EtOAc/cyclohexane, and filtered. The residues were combined. LCMS t = 3.81 mins [MH$^+$] 419/421.

6-[2-(5-Chloro-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-picolinic acid methyl ester

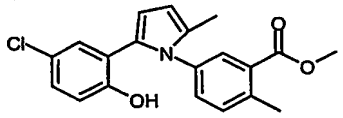


A solution of the acid (400mg, 0.95mmol), and thionyl chloride (173µL, 2.38mmol) in methanol (5mL) was stirred at reflux for 3 hours, under N_2. The reaction mixture was evaporated to dryness, and the residue dissolved in CH_2Cl_2. The solution was washed with 2N NaOH(aq). The organics were evaporated to dryness yielding the product was as a brown solid (217mg, 0.50mmol, 53%).
^{1}H NMR ($CDCl_3$): δ 2.38 (3H, s), 3.94 (3H, s), 4.69 (2H, s), 6.13 (1H, d, J=3Hz), 6.35 (1H, d, J = 3.26Hz), 6.61 (1H, d J = 8Hz), 7.05-7.09 (3H, m), 7.25-7.30 (5H, m, excess), 7.64 (1H, t, J=7.8Hz), 7.97 (1H, d, J = 7.5Hz).

The following compound was prepared by a similar route to 6-[2-(5-chloro-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-picolinic acid methyl ester from the appropriate intermediates

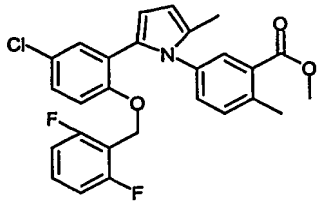
Structure	Name	LCMS
	3-[2-(5-Chloro-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-6-methyl-benzoic acid methyl ester	t = 4.13 [MH^+] 446/448

3-[2-(5-Chloro-2-hydroxy-phenyl)-5-methyl-pyrrol-1-yl]-6-methyl-benzoic acid methyl ester



The benzyl ether (2g, 4.49mmol) was dissolved in ethanol (50mL), and the solution was added to $Pd(OH)_2$ (20% on carbon, 150mg) under N_2. Hydrogenation was carried out over 75 minutes (130mL H_2). The reaction mixture was filtered through Celite®, washed through with ethanol, and evaporated to a red oil. The residue was purified by chromatography using a Biotage® 25S eluting with cyclohexane containing a gradient of 0-3% EtOAc. This yielded the title compound as a yellow oil (846mg, 2.38mmol, 53%).
LCMS t = 3.64 mins [MH^+] 356/358

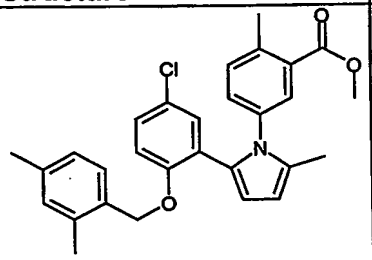
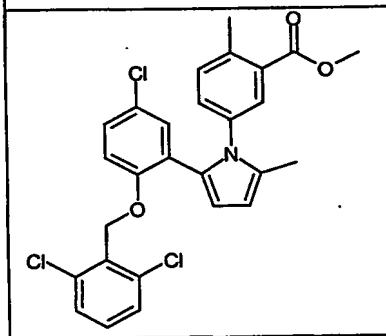
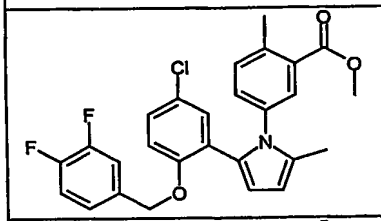
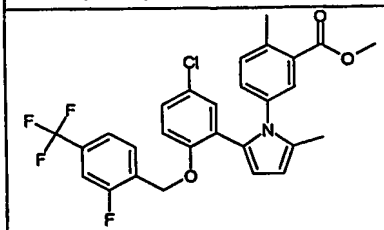
3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester

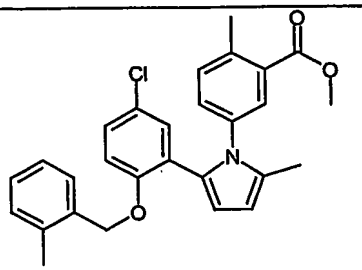
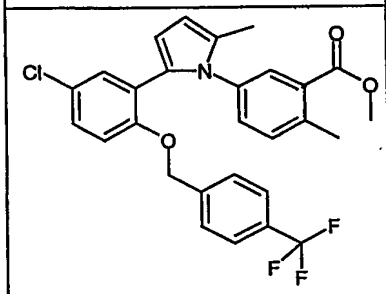
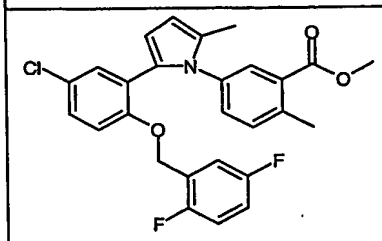
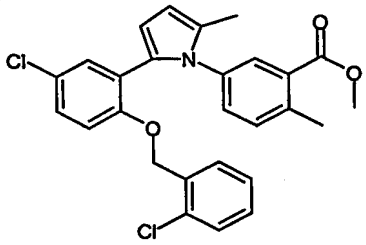
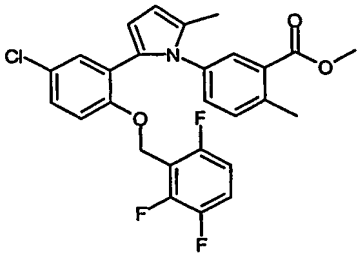


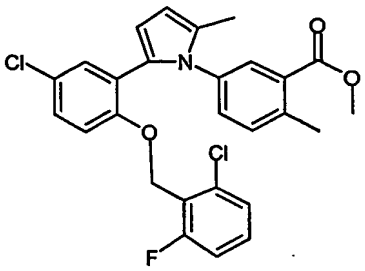
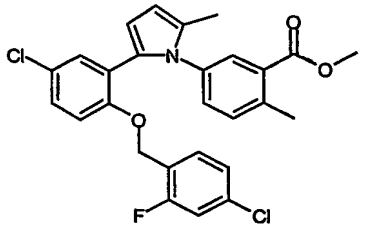
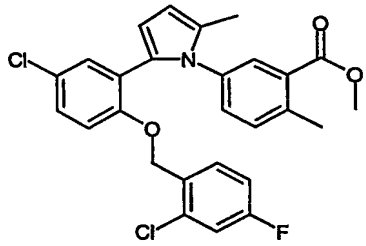
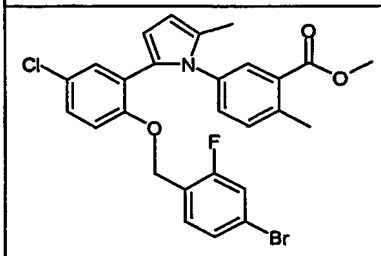
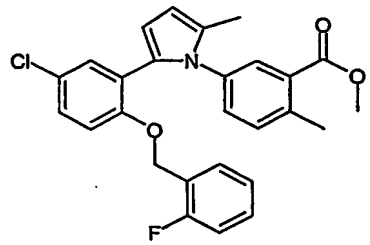
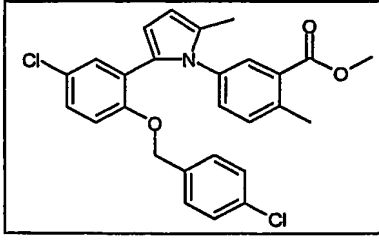
The phenol (141mg, 0.397mmol) and the 2,6-difluoro benzyl bromide (82mg, 0.397mmol) were heated with potassium carbonate (110mg, 0.794mmol) to 60°C in DMF (1mL) for 16 hours. The reaction mixture was diluted with H_2O, and extracted twice with Et_2O. The

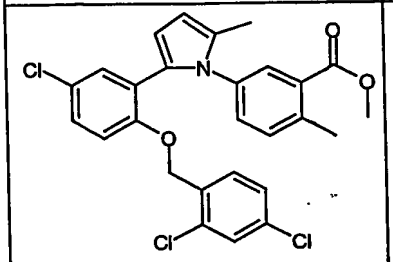
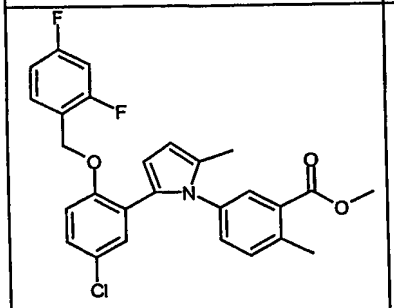
organics were collected, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by chromatography using an SPE silica cartridge (5g) eluting with cyclohexane containing a gradient of 0-5% EtOAc. This yielded the title compound as a clear oil (108mg, 0.225mmol, 57%). LCMS t = 4.08 [MH^+] 482/484.

The following esters were prepared by a similar route to 3-{2-[5-chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester from the appropriate intermediates.

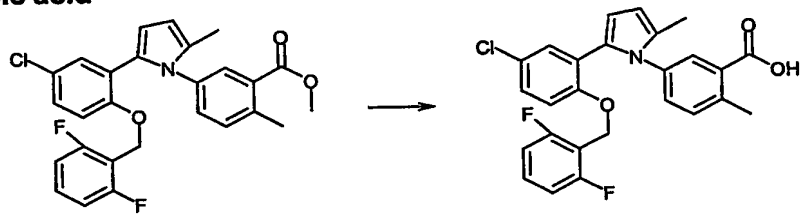
Structure	Name	LCMS
	3-{2-[5-Chloro-2-(2,4-dimethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.28 [MH^+] 474/476
	3-{2-[5-Chloro-2-(2,6-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.24 [MH^+] 514/516/518/520
	3-{2-[5-Chloro-2-(3,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.17 [MH^+] 482/484
	3-{2-[5-Chloro-2-(2-fluoro-4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.29 [MH^+] 532/534

	3-{2-[5-Chloro-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.22 [MH^+] 460/462
	3-{2-[5-Chloro-2-(4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.27 [MH^+] 514/516
	3-{2-[5-Chloro-2-(2,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.30 [MH^+] 482/484
	3-{2-[5-Chloro-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.41 [MH^+] 480/482/484
	3-{2-[5-Chloro-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.23 [MH^+] 500/502

	3-{2-[5-Chloro-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.31 [MH$^+$] 498/500/502
	3-{2-[5-Chloro-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.30 [MH$^+$] 498/500/502
	3-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.31 [MH$^+$] 498/500/502
	3-{2-[5-Chloro-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.32 [MH$^+$] 542/544/546
	3-{2-[5-Chloro-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.14 [MH$^+$] 464/466
	3-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.24 [MH$^+$] 480/482/484

	3-{2-[5-Chloro-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.41 [MH$^+$] 514/516/518/520
	3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid methyl ester	t = 4.14 [MH$^+$] 482/484

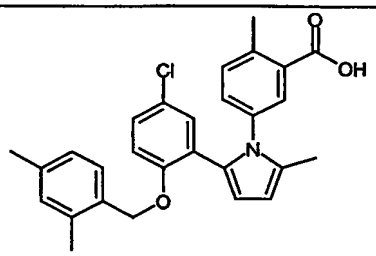
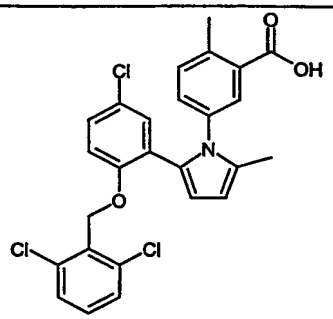
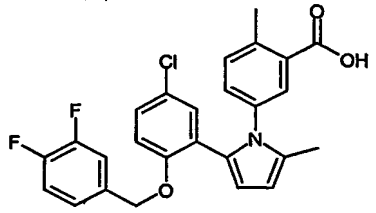
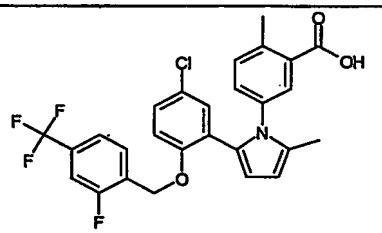
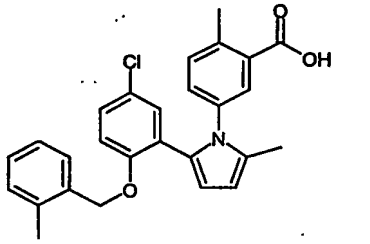
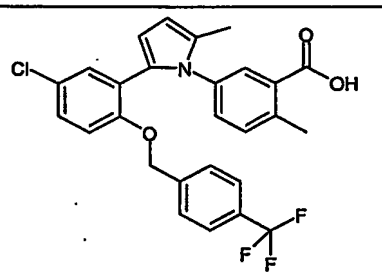
Example 2: 3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid

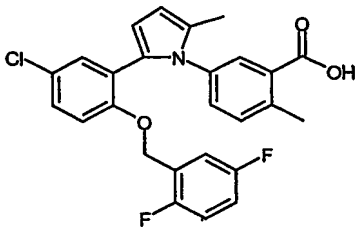
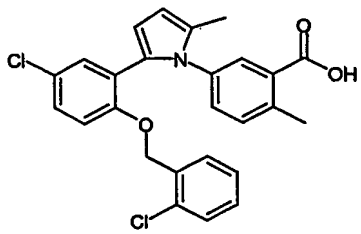
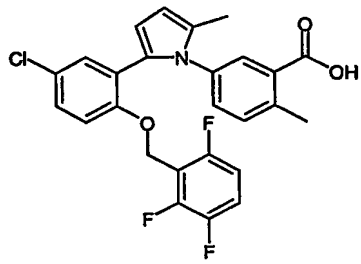
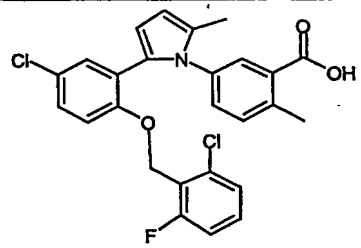
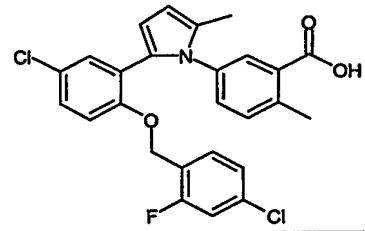
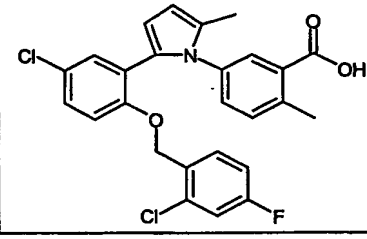


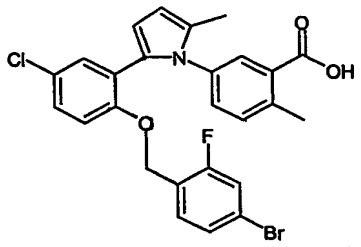
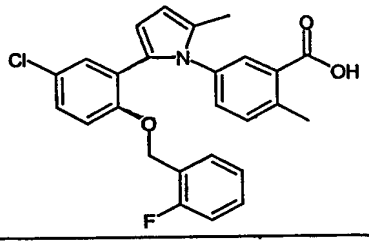
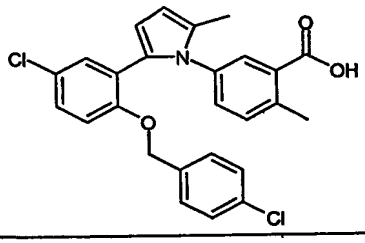
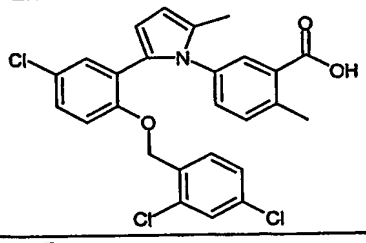
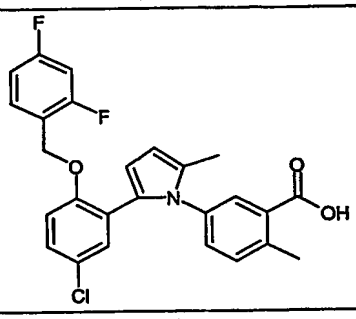
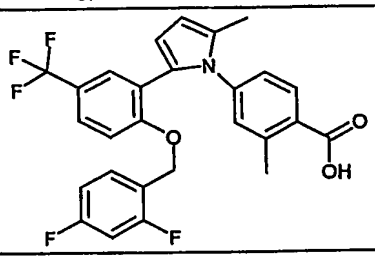
The methyl ester (108mg, 0.225mmol) was heated in EtOH (2mL) with 2N NaOH (0.5mL, aq) to 120°C for 5 minutes in the microwave. The reaction mixture was diluted with CH_2Cl_2, shaken with 2N HCl (aq), and separated using a hydrophobic frit. The organics were evaporated to give the title compound as a red gum (64mg, 0.137mmol, 61%).
LCMS t = 3.89 min [MH$^+$] 468/470.

The following acids were prepared by a similar route to 3-{2-[5-chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid from the appropriate intermediates.

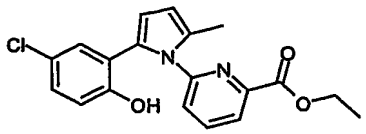
Example	Structure	Name	LCMS

3		3-{2-[5-Chloro-2-(2,4-dimethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.14 min [MH$^+$] 460/462
4		3-{2-[5-Chloro-2-(2,6-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.11min [MH$^+$] 500/502/504/506
5		3-{2-[5-Chloro-2-(3,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 3.99 min [MH$^+$] 468/470
6		3-{2-[5-Chloro-2-(2-fluoro-4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.11 min [MH$^+$] 518/520
7		3-{2-[5-Chloro-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.03 min [MH$^+$] 446/448
8		3-{2-[5-Chloro-2-(4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.10 min [MH$^+$] 500/502

9		3-{2-[5-Chloro-2-(2,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 3.96 min [MH^+] 468/470
10		3-{2-[5-Chloro-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.08 min [MH^+] 466/468/470
11		3-{2-[5-Chloro-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 3.89 min [MH^+] 486/488
12		3-{2-[5-Chloro-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.00 min [MH^+] 484/486/488
13		3-{2-[5-Chloro-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.18 min [MH^+] 484/486/488
14		3-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.17 min [MH^+] 484/486/488

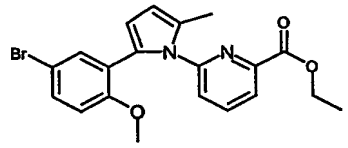
15		3-{2-[5-Chloro-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.22 min [MH$^+$] 528/530/532
16		3-{2-[5-Chloro-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.01 min [MH$^+$] 450/452
17		3-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.11 min [MH$^+$] 466/468/470
18		3-{2-[5-Chloro-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.30 min [M$^+$] 500/502/504/506
19		3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 3.99 min [MH$^+$] 468/470
20		4-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-6-methyl-benzoic acid	t = 4.04 min [MH$^+$] 502

6-[2-(5-Chloro-2-hydroxy-phenyl)-5-methyl-pyrrol-1-yl]-picolinic acid ethyl ester



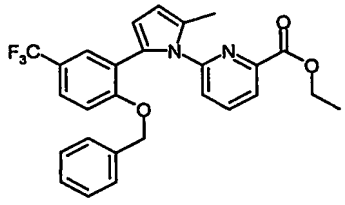
The benzyl ether (300mg, 0.693mmol) was dissolved in ethanol (10mL). The solution was added to palladium hydroxide (100mg) under N_2. Hydrogenation was carried out over 3 hours (16 mL of H_2 consumed). LCMS showed some remaining starting material. The solution was filtered through Celite, and added to fresh catalyst (100mg), under N_2. Hydrogenation was continued for 1.5 hours. LCMS showed no remaining starting material. The reaction mixture was filtered through Celite, and evaporated to dryness. ^{1}H NMR ($CDCl_3$) showed a mixture of methyl and ethyl esters had formed. The crude product was stirred with EtOH (10mL) with potassium carbonate (3eq, 308mg) at 40°C to convert all product to ethyl ester form. LCMS confirmed this process was complete. The crude product was purified using column chromatography (SPE, 10g, Si) eluting with 5% EtOAc/20% CH_2Cl_2/75% cyclohexane, to give the product as brown gum (121mg, 0.353mmol, 51%). LCMS t = 3.95 mins [MH^+] 337 and 449

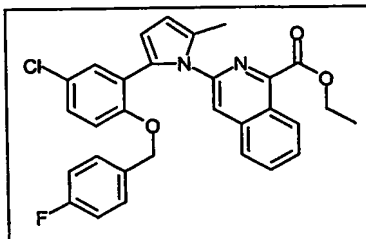
6-{2-[5-Bromo-2-methoxy-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester



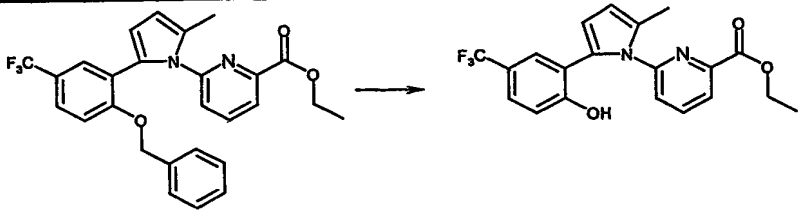
A mixture of 6-{2-[5-bromo-2-methoxy-phenyl]-5-methyl-pyrrol-1-yl}-2-bromo-pyridine (1.15g, 2.73mmol), $Pd(PPh_3)_2Cl_2$ (96mg, 0.14mmol), triethylamine (2.25ml) and ethanol (7.5ml) were saturated with carbon monoxide gas. The mixture was then heated under reflux, under a carbon monoxide atmosphere for 16 hours. Upon cooling, volatiles were removed *in vacuo* and the crude oil was purified by chromatography using Biotage® with *iso*hexane / EtOAc (7-25%) as eluant, to give the title compound (710mg, 63%). LCMS t = 3.63 [MH^+] 415/417.

The following esters were prepared by a similar route to 6-{2-[5-bromo-2-methoxy-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester from the appropriate intermediates.

Structure	Name	LCMS
	6-{2-[5-Trifluoromethyl-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 3.99 [MH^+] 481

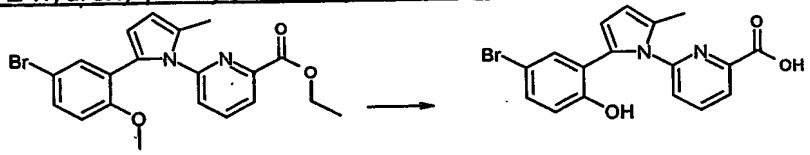
	3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isoquinoline-1-carboxylic acid ethyl ester	t = 4.22 [MH$^+$] 515/517

3-[2-(5-Trifluoromethyl-2-hydroxy-phenyl)-5-methyl-pyrrol-1-yl]-picolinic acid ethyl ester



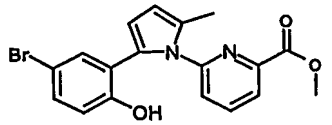
3-[2-(5-Trifluoromethyl-2-benzyloxy-phenyl)-5-methyl-pyrrol-1-yl]-picolinic acid ethyl ester (0.32g, 0.7mmol), palladium on charcoal (10% containing 50% water) (71mg), ammonium formate (0.21g, 3.3mmol) and EtOH (5ml) were stirred at 60°C under a nitrogen atmosphere for 1 hour. Upon cooling the mixture was filtered and the solvent removed *in vacuo*. The residue was purified by chromatography using a Biotage® 40M eluting with 10% EtOAc/iso-hexane to yield the title compound as a yellow oil (0.226g, 87%)
LCMS t = 3.46 [MH$^+$] 391

6-[2-(5-Bromo-2-hydroxy-phenyl)-5-methyl-pyrrol-1-yl]-picolinic acid



6-{2-[5-Bromo-2-methoxy-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester (980mg, 2.36 mmol) and sodium methanethiolate (830mg, 11.8mmol) in DMF (75ml) were heated at 100°C for 4 hours. Upon cooling, the mixture was diluted with 2M HCl (250ml) and extracted with EtOAc (3x150ml). The organics were washed with water (2x50ml), brine (50ml), dried ($MgSO_4$), filtered and concentrated to give the title compound as a yellow oil (1.2g). LCMS t = 3.84 min [MH$^+$] 373/375.

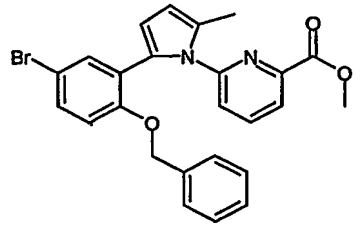
6-[2-(5-Bromo-2-hydroxy-phenyl)-5-methyl-pyrrol-1-yl]-picolinic acid methyl ester



6-[2-(5-Bromo-2-hydroxy-phenyl)-5-methyl-pyrrol-1-yl]-picolinic acid (1g) and conc. sulfuric acid (0.2ml) in methanol (10ml) were heated at 55°C for 5 hours. Upon cooling, aq NH_3 solution (.880) (2ml) was added and the mixture concentrated *in vacuo*. The residue was partitioned between 2M HCl (50ml) and EtOAc (50ml). The organic layer was washed with

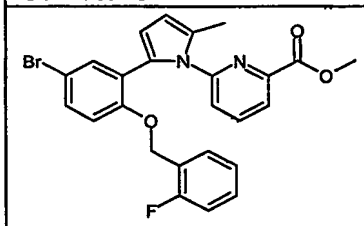
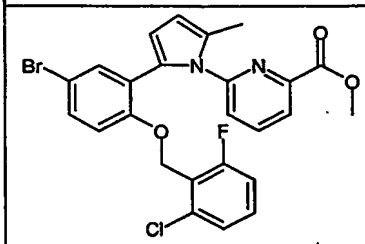
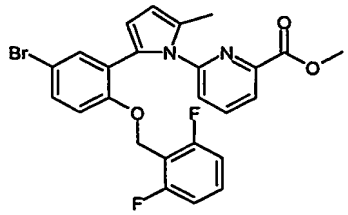
brine, dried ($MgSO_4$) filtered and concentrated. The residue was purified by chromatography using Biotage with *iso*-hexane containing a gradient of EtOAc (10-50%) to give the title compound as an oil (550mg). LCMS t = 3.26 min [MH^+] 387/389

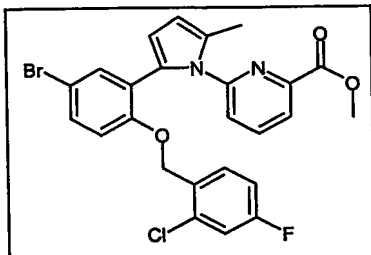
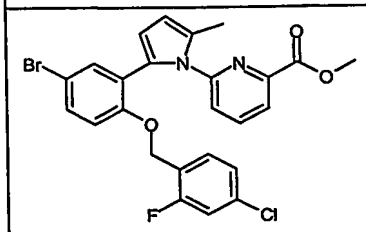
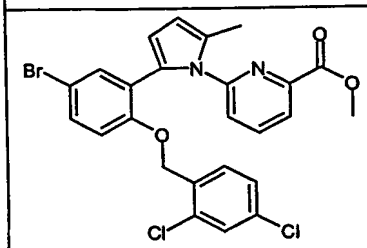
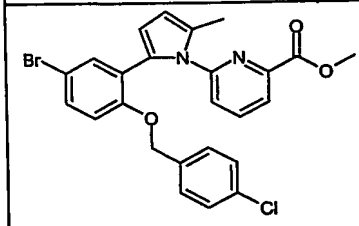
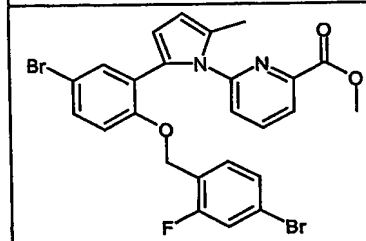
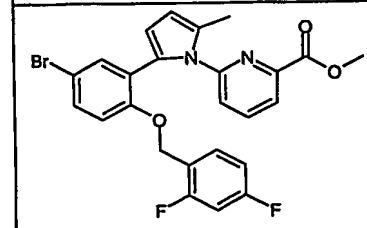
6-{2-[5-Bromo-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid methyl ester

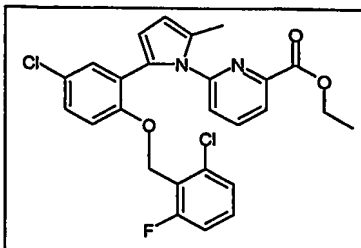
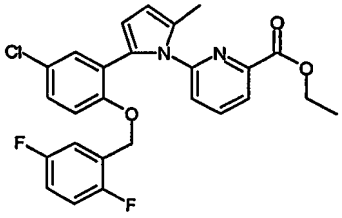
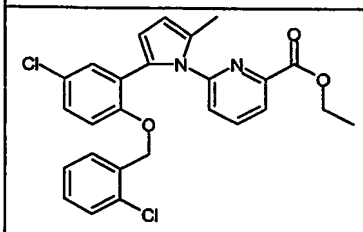
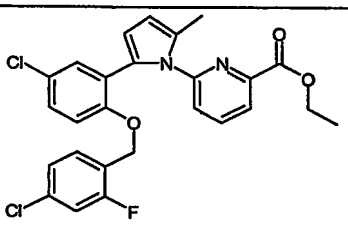
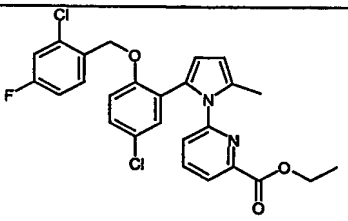
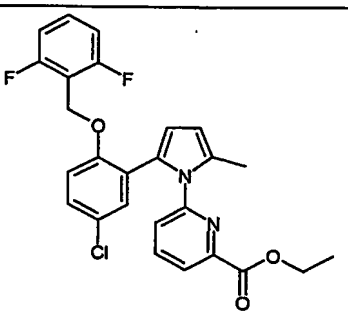


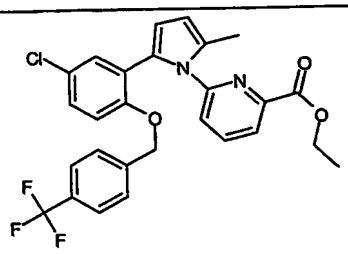
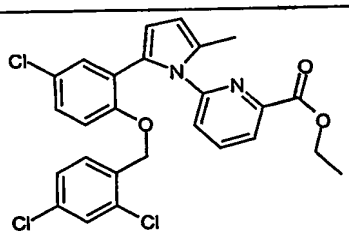
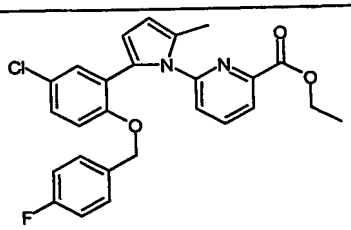
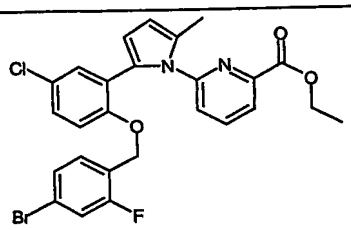
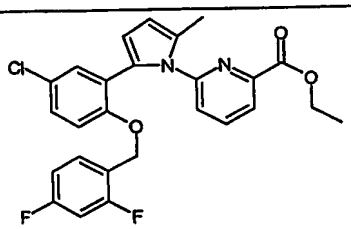
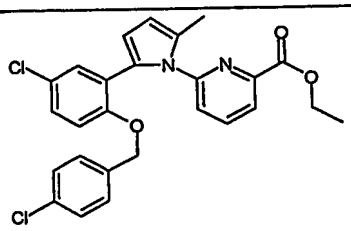
6-[2-(5-Bromo-2-hydroxy-phenyl)-5-methyl-pyrrol-1-yl]-picolinic acid methyl ester (0.11g, 0.28mmol), benzyl bromide (0.035ml, 0.28mmol) and K_2CO_3 (0.43g, 0.31mmol) were heated in butan-2-one (4ml) under reflux for 16 hours. The mixture was cooled, diluted with CH_2Cl_2 (20ml) and shaken with water (2ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated. The residue was purified by chromatography using Biotage®, with *iso*-hexane / EtOAc (10-15%) as eluant, to give the title compound. LCMS t = 3.89 [MH^+] 477/479.

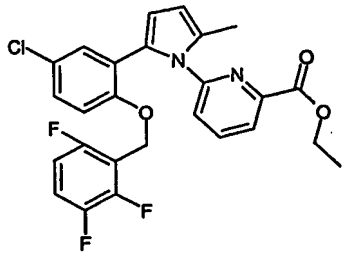
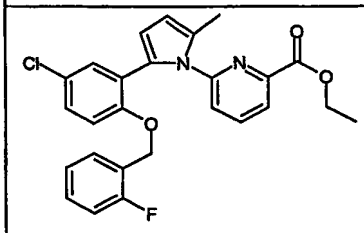
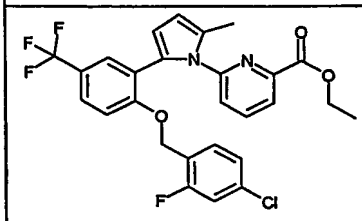
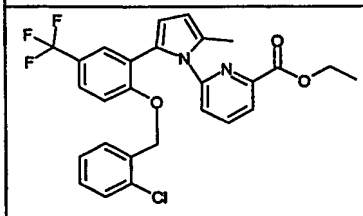
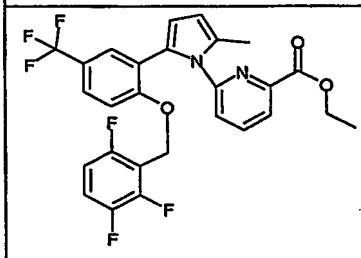
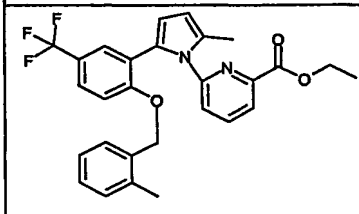
The following esters were prepared by a similar route to 6-{2-[5-bromo-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid methyl ester from the appropriate intermediates.

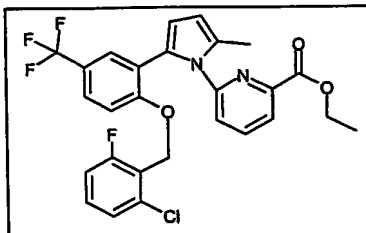
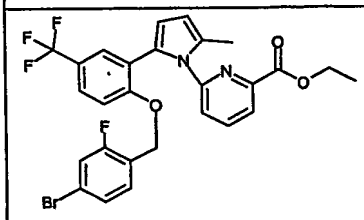
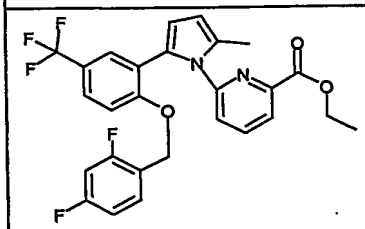
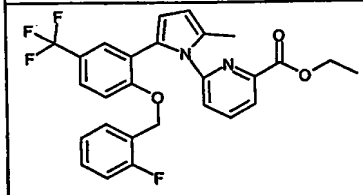
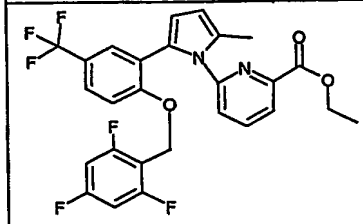
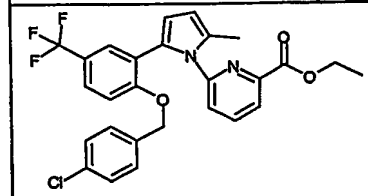
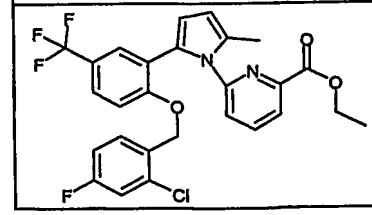
Structure	Name	LCMS
	6-{2-[5-Bromo-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid methyl ester	t = 3.91 [MH^+] 495/497
	6-{2-[5-Bromo-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid methyl ester	t = 3.96 [MH^+] 529/531/533
	6-{2-[5-Bromo-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid methyl ester	t = 3.85 [MH^+] 513/515

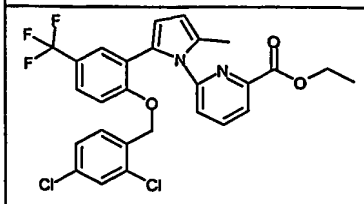
	6-{2-[5-Bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid methyl ester	t = 4.12 [MH$^+$] 529/531/533
	6-{2-[5-Bromo-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid methyl ester	t = 4.10 [MH$^+$] 529/531/533
	6-{2-[5-Bromo-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid methyl ester	t = 4.29 [MH$^+$] 545/547/549/551
	6-{2-[5-Bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid methyl ester	t = 4.07 [MH$^+$] 511/513/515
	6-{2-[5-Bromo-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid methyl ester	t = 4.15 [MH$^+$] 573/575/577
	6-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid methyl ester	t = 3.95 [MH$^+$] 513/515

	6-{2-[5-Chloro-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 3.99 min [MH$^+$] 499/501/503
	6-{2-[5-Chloro-2-(2,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 3.98 [MH$^+$] 483/485
	6-{2-[5-Chloro-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.07 min [MH$^+$] 481/483/485
	6-{2-[5-Chloro-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.09 min [MH$^+$] 499/501/503
	6-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.19 min [MH$^+$] 499/501/503
	6-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 3.91 min [MH$^+$] 483/485

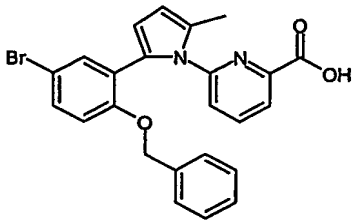
	6-{2-[5-Chloro-2-(4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.01 min [MH$^+$] 515/517
	6-{2-[5-Chloro-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.27 [MH$^+$] 515/517/519/521
	6-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 3.96 min [MH$^+$] 465/467
	6-{2-[5-Chloro-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.14 min [MH$^+$] 543/545/547
	6-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 3.99 [MH$^+$] 483/485
	6-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.09 min [MH$^+$] 481/483/485

	6-{2-[5-Chloro-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 3.84 [MH$^+$] 501/503
	6-{2-[5-Chloro-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 3.96 [MH$^+$] 465/467
	6-{2-[5-Trifluoromethyl-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.14 [MH$^+$] 533/535
	6-{2-[5-Trifluoromethyl-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.13 [MH$^+$] 515/517
	6-{2-[5-Trifluoromethyl-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 3.96 [MH$^+$] 535
	6-{2-[5-Trifluoromethyl-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.08 [MH$^+$] 495

	6-{2-[5-Trifluoromethyl-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.08 [MH$^+$] 535/533
	6-{2-[5-Trifluoromethyl-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.08 [MH$^+$] 577/579
	6-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.10 [MH$^+$] 517
	6-{2-[5-Trifluoromethyl-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 3.99 [MH$^+$] 499
	6-{2-[5-Trifluoromethyl-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 3.99 [MH$^+$] 535
	6-{2-[5-Trifluoromethyl-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.14 [MH$^+$] 515/517
	6-{2-[5-Trifluoromethyl-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.18 [MH$^+$] 533/535

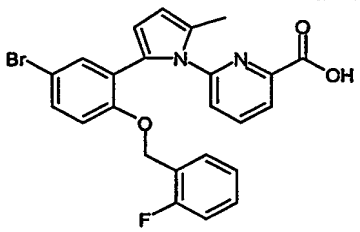
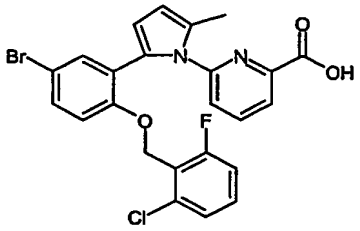
	6-{2-[5-Trifluoromethyl-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid ethyl ester	t = 4.34 [MH$^+$] 549/551/553

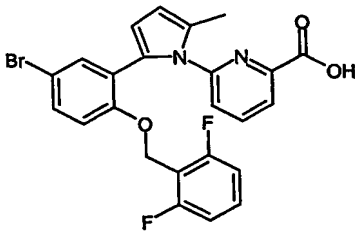
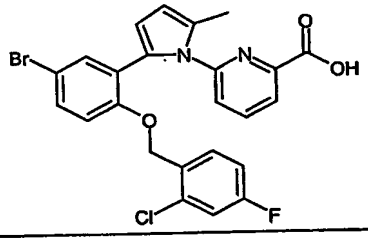
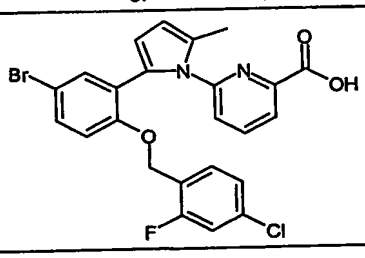
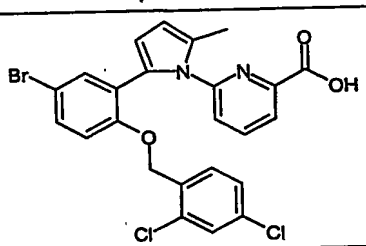
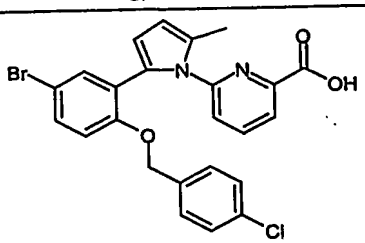
Example 21: 6-{2-[5-Bromo-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid

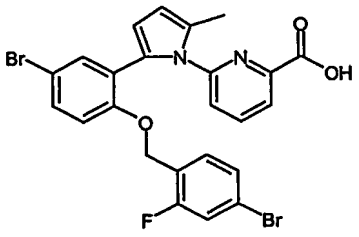
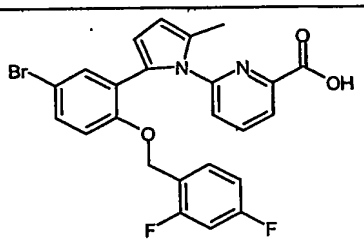
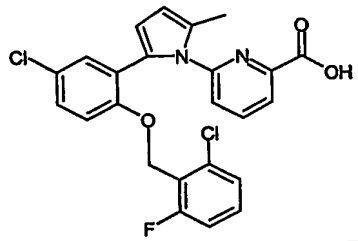
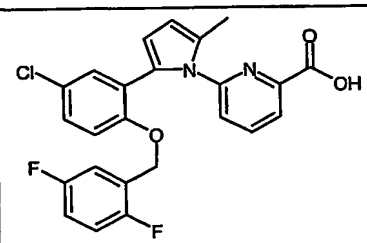
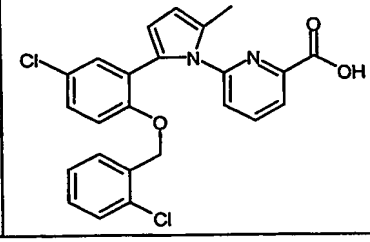


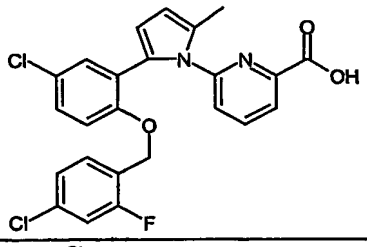
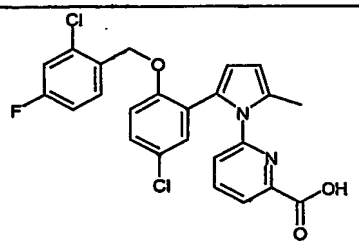
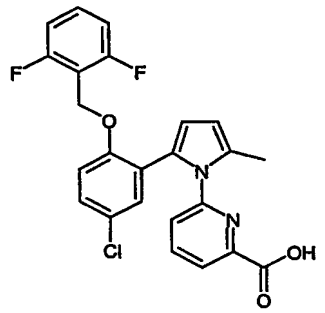
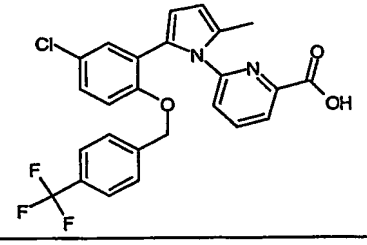
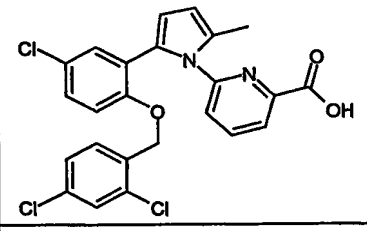
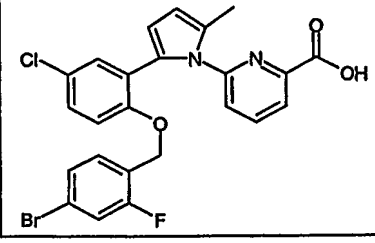
6-{2-[5-Bromo-2-benzyloxy-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid (150mg) was dissolved in ethanol (5ml) and 2M NaOH (1ml) and was heated in a sealed vessel at 120°C for 15 minutes using microwaves. Upon cooling the reaction was diluted with CH_2Cl_2 (20ml) and shaken with dil. HCl (3ml). The organics were separated using a phase separator column with a $NaSO_4$ cartridge attached and concentrated to give the title compound. LCMS t = 3.97 min [MH$^+$} 463/465

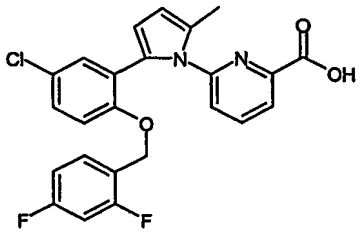
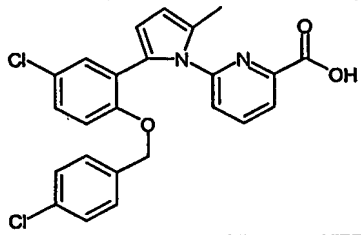
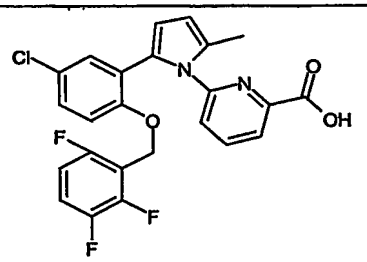
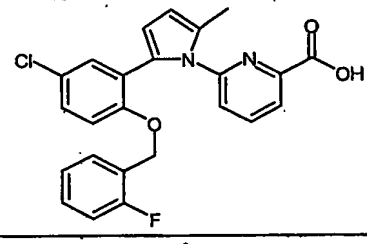
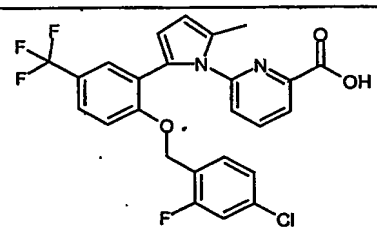
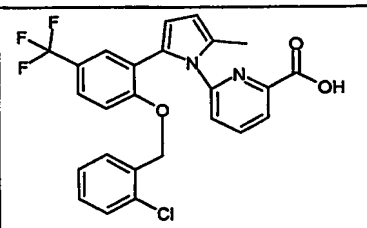
The following acids were prepared by a similar route to 6-{2-[5-bromo-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic-acid from the appropriate intermediates.

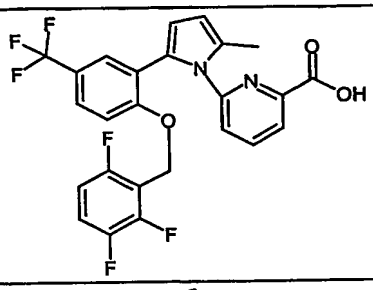
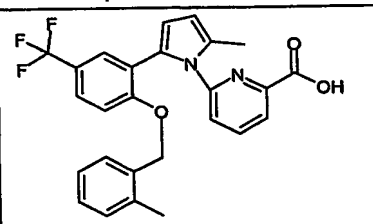
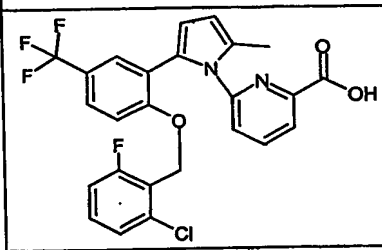
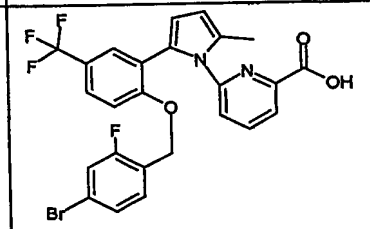
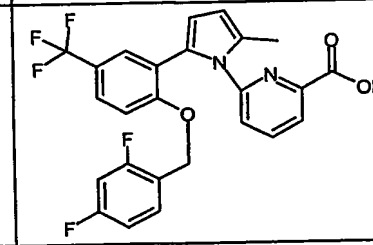
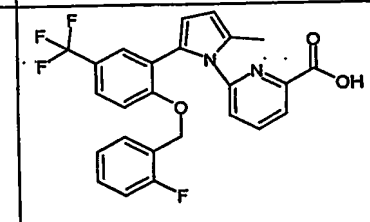
Examples	Structure	Name	LCMS/NMR Data
22		6-{2-[5-Bromo-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.98 min [MH$^+$} 481/483
23		6-{2-[5-Bromo-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.93 min [MH$^+$} 515/517/519

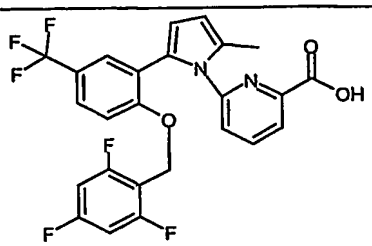
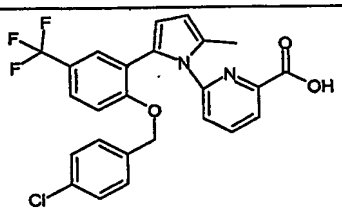
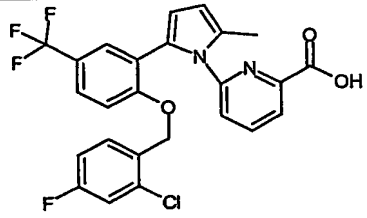
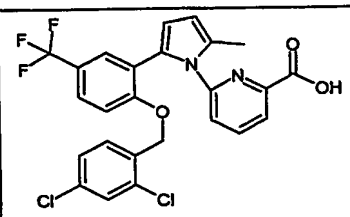
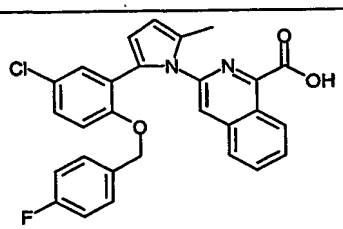
24		6-{2-[5-Bromo-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.82 min [MH$^+$} 499/501 ^{1}H NMR (400MHz, $CDCl_3$) 2.28(3H, s), 4.66 (2H, s), 6.11 (1H, d, J=3Hz), 6.26 (1H, d, J=3Hz), 6.77 (1H, d, J=8Hz), 6.83-6.90 (2H, m), 7.06 (1H, d, J=8Hz), 7.27-7.37 (2H, m), 7.47 (1H, apparent s), 7.76 (1H, t, J=8Hz), 8.01 (1H, d, J=8Hz)
25		6-{2-[5-Bromo-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.08 min [MH$^+$} 515/517/519
26		6-{2-[5-Bromo-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.06 min [MH$^+$} 515/517/519
27		6-{2-[5-Bromo-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.26 min [MH$^+$} 531/533/535/537
28		6-{2-[5-Bromo-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.04 min [MH$^+$} 497/499/501

29		6-{2-[5-Bromo-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.24 min [MH^+} 559/561/563 ^1H NMR (400MHz, $CDCl_3$) 2.33 (3H, s), 4.58 (2H, s), 6.17 (1H, d, J=3Hz), 6.31 (1H, d, J=3Hz), 6.61 (1H, d, J=8Hz), 6.88 (1H, t, J=8Hz), 7.09 (1H, d, J=8Hz), 7.18-7.24 (2H, m), 7.28-7.34 (1H, m), 7.48 (1H, apparent s), 7.78 (1H, t, J=8Hz), 8.03 (1H, d, J=8Hz)
30		6-{2-[5-Bromo-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.99 min [MH^+} 499/501
31		6-{2-[5-Chloro-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.88 min [MH^+] 471/473/475
32		6-{2-[5-Chloro-2-(2,5-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.88 min [MH^+] 455/457
33		6-{2-[5-Chloro-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.03 min [MH^+] 453/455/457

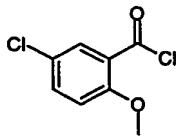
34		6-{2-[5-Chloro-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.09 min [MH$^+$] 471/473/475
35		6-{2-[5-Chloro-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.01 min [MH$^+$] 471/473/475
36		6-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.76 min [MH$^+$] 455/457
37		6-{2-[5-Chloro-2-(4-trifluoromethyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.94 min [MH$^+$] 487/489
38		6-{2-[5-Chloro-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.19 min [MH$^+$] 487/489/491/493
39		6-{2-[5-Chloro-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.05 min [MH$^+$] 515/517/519

40		6-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.86 min [MH^+] 455/457
41		6-{2-[5-Chloro-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.98 min [MH^+] 453/455/457
42		6-{2-[5-Chloro-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.75 min [MH^+] 473/475
43		6-{2-[5-Chloro-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.85 min [MH^+] 437/439
44		6-{2-[5-Trifluoromethyl-2-(2-fluoro-4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.00 min [MH^+] 505/507
45		6-{2-[5-Trifluoromethyl-2-(2-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.09 min [MH^+] 487/489

46		6-{2-[5-Trifluoromethyl-2-(2,3,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.81 min [MH^+] 507
47		6-{2-[5-Trifluoromethyl-2-(2-methyl-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.98 min [MH^+] 467
48		6-{2-[5-Trifluoromethyl-2-(2-chloro-6-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.92 min [MH^+] 505/507
49		6-{2-[5-Trifluoromethyl-2-(2-fluoro-4-bromo-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.13 min [MH^+] 549/551
50		6-{2-[5-Trifluoromethyl-2-(2,4-difluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.90 min [MH^+] 489
51		6-{2-[5-Trifluoromethyl-2-(2-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.88 min [MH^+] 471 ^1H NMR (400MHz, $CDCl_3$) 2.32 (3H, s), 4.74 (2H, s), 6.09 (1H, d, J=3Hz), 6.38 (1H, d, J=3Hz), 6.84 (1H, d, J=8Hz), 7.00-7.12 (4H, m), 7.27 (1H, m), 7.48 (1H, dd, J=8Hz, 2Hz), 7.60 (1H, d,

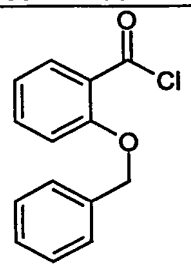
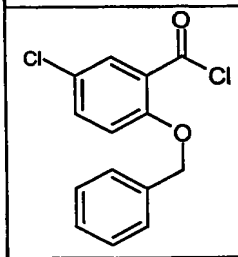
			J=2Hz), 7.77 (1H, t, J=8Hz), 8.02 (1H, d, J=8Hz)
52		6-{2-[5-Trifluoromethyl-2-(2,4,6-trifluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 3.85 min [MH^+] 507 ^1H NMR (400MHz, $CDCl_3$) 2.29 (3H, s), 4.72 (2H, s), 6.14 (1H, d, J=3Hz), 6.32 (1H, d, J=3Hz), 6.63-6.71 (2H, m), 6.95 (1H, d, J=8Hz), 7.48-7.55 (2H, m), 7.27 (1H, m), 7.81 (1H, t, J=8Hz), 8.04 (1H, d, J=8Hz)
53		6-{2-[5-Trifluoromethyl-2-(4-chloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.06 min [MH^+] 487/489
54		6-{2-[5-Trifluoromethyl-2-(2-chloro-4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.04 min [MH^+] 505/507
55		6-{2-[5-Trifluoromethyl-2-(2,4-dichloro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-picolinic acid	t = 4.26 min [MH^+] 521/523/524
56		3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-methyl-pyrrol-1-yl}-isoquinoline-1-carboxylic acid	t = 4.40 [MH^+] 487/489

5-Chloro-2-methoxy-benzoyl chloride

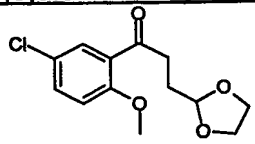


Thionyl chloride (7.8mL, 0.108mol) was added dropwise to a solution of 5-chloro-2-methoxy-benzoic acid (10g, 0.054mol) in anhydrous CH_2Cl_2 (54mL). The reaction was heated to reflux and stirred under nitrogen for 23 hours. The reaction mixture was allowed to cool and reduced *in vacuo*. The acid chloride was used immediately in the next stage.

The following acid chlorides were prepared by a similar route to 5-chloro-2-methoxy-benzoyl chloride from the appropriate intermediates and used immediately in their respective next stage.

Structure	Name
	2-Benzyloxy-benzoyl chloride
	2-Benzyloxy-5-chloro-benzoyl chloride

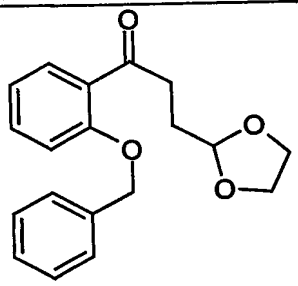
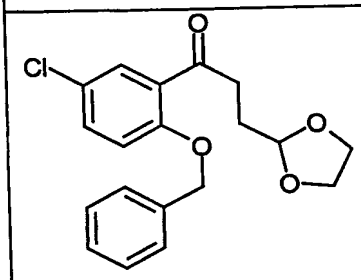
1-(5-Chloro-2-methoxy-phenyl)-3-[1,3]dioxolan-2-yl-propan-1-one



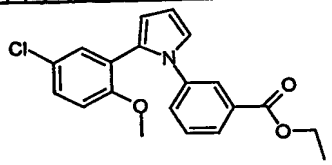
2-(2-bromoethyl)-1,3-dioxolane (0.008mol, 1mL) was added dropwise to a suspension of magnesium turnings (0.113mol, 2.73g) in anhydrous THF (40mL) under nitrogen. The reaction was heated to 50°C before the dropwise addition of further 2-(2-bromoethyl)-1,3-dioxolane (0.048mol, 5.61mL), maintaining a constant reflux. After complete addition the reaction was cooled to 0°C, and then transferred *via* a cannula over a period of 25 minutes to a pre-cooled (-65°C) solution of 5-chloro-2-methoxy-benzoyl chloride (0.054mol) in anhydrous THF (40mL), maintaining the reaction temperature in the range -45°C to –65. After complete addition, the reaction was allowed to slowly rise in temperature to -4°C over a period of 2 hours, before the addition of water (20mL). The aqueous layer was separated, and extracted with EtOAc (2 x 100mL). The extracts were combined with the

organic layer, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The oil was purified by flash silica column chromatography (cyclohexane to 15% EtOAc in cyclohexane) to afford the title compound as a cream solid (1.58g, 11%).
^1H NMR ($CDCl_3$) - δ2.08 (dt, 2H), 3.09 (t, 2H), 3.90 (m, 7H), 6.90 (d, 1H), 7.39 (dd, 1H), 7.65 (d, 1H).

The following dioxolanes were prepared by a similar route to 1-(5-chloro-2-methoxy-phenyl)-3-[1,3]dioxolan-2-yl-propan-1-one from the appropriate intermediates.

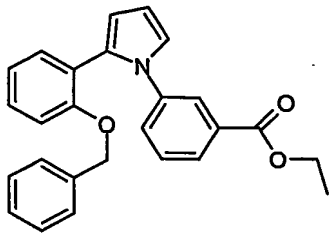
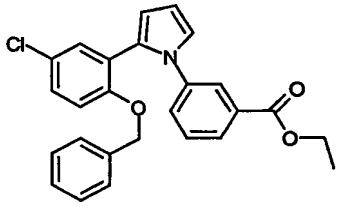
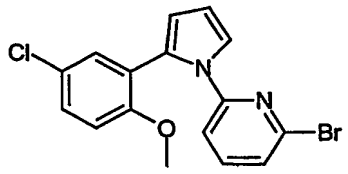
Structure	Name	Data
	1-(2-Benzyloxy-phenyl)-3-[1,3]dioxolan-2-yl-propan-1-one	^1H NMR ($CDCl_3$) δH 2.00-2.10 (2H, m), 3.12 (2H , t), 3.74-3.87 (4H, m), 4.99 (1H, t), 5.16 (2H, s), 6.95 (2H, m), 7.29-7.56 (6H, m), 7.70 (1H, dd).
	1-(2-Benzyloxy-5-chloro-phenyl)-3-[1,3]dioxolan-2-yl-propan-1-one	

3-[2-(5-Chloro-2-methoxy-phenyl)-pyrrol-1-yl]-benzoic acid ethyl ester

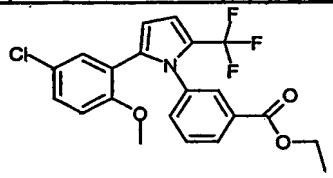


A solution of 1-(5-chloro-2-methoxy-phenyl)-3-[1,3]dioxolan-2-yl-propan-1-one (1.58g, 5.82mmol), ethyl-3-aminobenzoate (6.4 mmol, 0.96mL) and pTSA (cat) in anhydrous 1-methyl-2-pyrrolidinone (6mL) were heated in a microwave reactor for 12 minutes at 150°C. The reaction mixture was diluted with EtOAc (100mL) and washed with 2N HCl (25mL) and saturated $NaHCO_3$ (25mL), dried ($MgSO_4$) and concentrated *in vacuo*. The oil was purified by silica chromatography (cyclohexane to 5% EtOAc in cyclohexane) to yield the title compound as an orange oil (0.91g, 44%).
^1H NMR ($CDCl_3$) - δ1.37 (t, 3H), 3.24 (s, 3H), 4.35 (q, 2H), 6.40 (m, 2H), 6.60 (d, 1H), 7.04 (dd, 1H), 7.20 (dd, 1H), 7.23 (ddd, 1H), 7.31 (dd, 1H), 7.35 (d, 1H), 7.89 (m, 2H).

The following pyrroles were prepared by a similar route to 3-[2-(5-chloro-2-methoxy-phenyl)-pyrrol-1-yl]-benzoic acid ethyl ester from the appropriate intermediates.

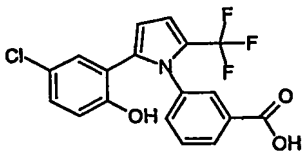
Structure	Name	LCMS
	3-[2-(2-Benzyloxy-phenyl)-pyrrol-1-yl]-benzoic acid ethyl ester	t = 4.03 min [MH^+] 398
	3-[2-(5-Chloro-2-benzyloxy-phenyl)-pyrrol-1-yl]-benzoic acid ethyl ester	t = 4.03 min [MH^+] 432/434
	2-Bromo-6-[2-(5-chloro-2-methoxy-phenyl)-pyrrol-1-yl]-pyridine	t = 3.74min [MH^+] 363/365/367

3-[2-(5-Chloro-2-methoxy-phenyl)-5-trifluoromethyl-pyrrol-1-yl]-benzoic acid ethyl ester



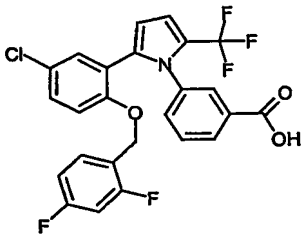
Iron (II) sulfate heptahydrate (1.12mmol, 0.310g) was added to a solution of 3-[2-(5-Chloro-2-methoxy-phenyl)-pyrrol-1-yl]-benzoic acid ethyl ester (0.66g, 1.86mmol) in anhydrous DMSO (10mL). Trifluoromethyl iodide was bubbled through the reaction for two minutes. Hydrogen peroxide (30% wt/wt aqueous solution, 1.26mL) was then added and the reaction was stirred at 22°C for 2 hours. The reaction was added to saturated aqueous sodium sulfite solution (100mL) and the suspension extracted with with diethyl ether (100mL). The ether extraction was dried ($MgSO_4$) and and concentrated *in vacuo*. The crude product was purified by silica chromatography (cyclohexane to 5% EtOAc in cyclohexane) to yield the title compound as an yellow oil (0.34g, 43%).
LCMS t = 3.94min [MH^+] 424

3-[2-(5-Chloro-2-hydroxy-phenyl)-5-trifluoromethyl-pyrrol-1-yl]-benzoic acid



Sodium thiomethoxide (4mmol, 0.28g) was added to a solution of 3-[2-(5-Chloro-2-methoxy-phenyl)-5-trifluoromethyl-pyrrol-1-yl]-benzoic acid ethyl ester (0.80mmol, 0.341g) in anhydrous dimethylformamide (7.5mL). The reaction was heated to 100°C and stirred for 4 hours. The reaction mixture was partitioned between 2N HCl (30mL) and EtOAc (50mL). The aqueous layer was separated and extracted with EtOAc (2 x 50mL). The EtOAc layers were combined, washed with brine (30mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by silica chromatography (Cyclohexane to CH_2Cl_2 to 30% EtOAc in CH_2Cl_2) to yield a yellow oil (0.26g, 85%).
^1H NMR ($CDCl_3$) - δ 6.42 (d, 1H), 6.77 (d, 1H), 6.86 (d, 1H), 6.89 (d, 1H), 7.09 (dd, 1H), 7.44 (m, 2H), 7.98 (s, 1H), 8.02 (m, 2H), 8.09 (m, 1H).

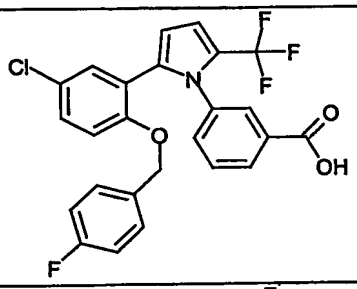
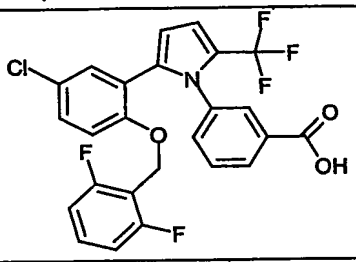
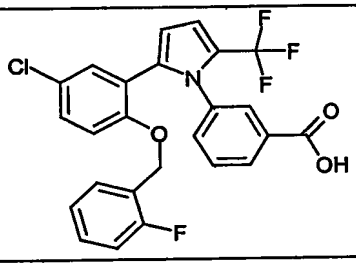
Example 57: 3-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-trifluoromethyl-pyrrol-1-yl}-benzoic acid



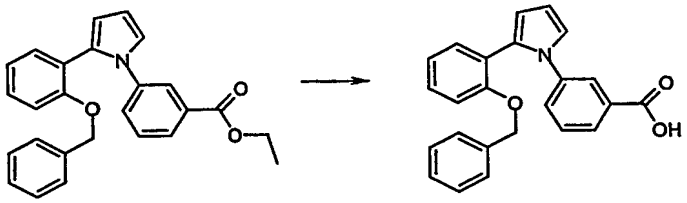
Potassium carbonate (0.37mmol, 65mg) and potassium iodide (0.034mmol, 5.6mg) was added to a solution of 3-[2-(5-chloro-2-hydroxy-phenyl)-5-trifluoromethyl-pyrrol-1-yl]-benzoic acid (0.17mmol, 0.065mg) in anhydrous MeOH (1.7mL). The reaction was heated to 60°C before the dropwise addition of 2,4-difluorobenzyl bromide (0.34mmol, 44μL). Heating was continued for one hour. The reaction was cooled, concetnrated *in vacuo* and partitioned between 2N HCl (2mL) and CH_2Cl_2 (2mL). The organic layer was collected and the solvent removed. The crude product was purified via MDAP to yield a white solid (42.3mg, 49%). LCMS t = 3.97min [MS-] 506/508.

The following acids were prepared by a similar route to 3-{2-[5-chloro-2-(2,4-difluoro-benzyloxy)-phenyl]-5-trifluoromethyl-pyrrol-1-yl}-benzoic acid from the appropriate intermediates.

Example	Structure	Name	LCMS

58		3-{2-[5-Chloro-2-(4-fluoro-benzyloxy)-phenyl]-5-trifluoromethyl-pyrrol-1-yl}-benzoic acid	t = 3.96min [MS-] 488/490
59		3-{2-[5-Chloro-2-(2,6-difluoro-benzyloxy)-phenyl]-5-trifluoromethyl-pyrrol-1-yl}-benzoic acid	t = 3.89min [MS-] 506/508
60		3-{2-[5-Chloro-2-(2-fluoro-benzyloxy)-phenyl]-5-trifluoromethyl-pyrrol-1-yl}-benzoic acid	t = 3.96min [MS-] 488/490

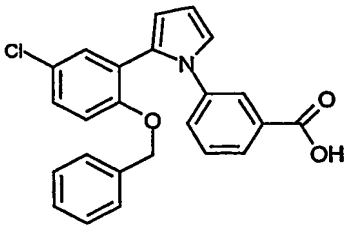
Example 61: 3-[2-(2-Benzyloxy-phenyl)-pyrrol-1-yl]-benzoic acid



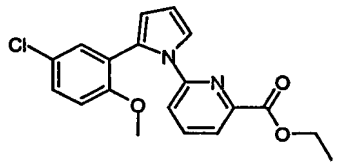
3-[2-(2-Benzyloxy-phenyl)-pyrrol-1-yl]-benzoic acid ethyl ester (0.046g, 0.1mmol) was heated in a mixture of ethanol (0.5mL) and 2M sodium hydroxide (1.5mL) at 100°C in a microwave for 2 minutes. Upon cooling, the mixture was diluted with CH_2Cl_2 and 2M HCl then filtered through a hydrophobic frit, fitted with a sodium sulfate cartridge, and evaporated to give the title compound. LCMS t = 3.78 min [MH^+] 370; [MH-] 368.

The following acids were prepared by a similar route to 3-[2-(2-benzyloxy-phenyl)-pyrrol-1-yl]-benzoic acid from the appropriate intermediates.

Example	Structure	Name	LCMS

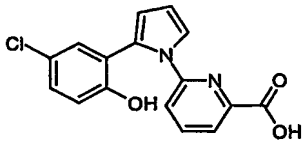
62		3-[2-(5-Chloro-2-benzyloxy-phenyl)-pyrrol-1-yl]-benzoic acid	t = 3.86 min [MH$^+$] 404/406; [MH-] 402/404

6-[2-(5-Chloro-2-methoxy-phenyl)-pyrrol-1-yl]-picolinic acid ethyl ester



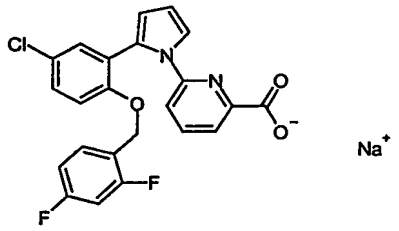
To a stirring solution of 2-bromo-6-[2-(5-chloro-2-methoxy-phenyl)-pyrrol-1-yl]-pyridine (0.16g, 0.4mmol) in anhydrous ethanol (1.3mL) was added triethylamine (0.4mL) and dichlorobis(triphenylphosphine) palladium (II) (5 mol%). The reaction was heated under a carbon monoxide atmosphere at 75°C for sixty-five hours. The reaction was reduced *in vacuo* and purified by silica chromatography (cyclohexane to 25% EtOAc in cyclohexane) to yield a yellow oil (48mg, 33%). LCMS t = 3.58min [MH$^+$] 357/359

6-[2-(5-Chloro-2-hydroxy-phenyl)-pyrrol-1-yl]-picolinic acid



To a stirring solution of 6-[2-(5-chloro-2-methoxy-phenyl)-pyrrol-1-yl]-picolinic acid ethyl ester (47mg, 0.132mmol) in anhydrous DMF (2mL) was added sodium thiomethoxide (0.66mmol, 46mg). The reaction was heated at 100°C for four hours, allowed to cool, then partitioned between EtOAc (50mL) and 2N HCl (30mL). The aqueous layer was separated and extracted with EtOAc (2 x 50mL). The organics were combined, dried ($MgSO_4$) and the solvent removed. The crude product was purified by silica chromatography (CH_2Cl_2 to 25% EtOAc in CH_2Cl_2) to yield a colourless glass (31mg, 74%). LCMS t = 3.62min [MH$^+$] 315/317.

Example 63: 6-{2-[5-Chloro-2-(2,4-difluoro-benzyloxy)-phenyl)-pyrrol-1-yl]-picolinic acid sodium salt



To a solution of 6-[2-(5-chloro-2-hydroxy-phenyl)-pyrrol-1-yl]-picolinic acid (0.098mmol, 30.8mg) in anhydrous methanol (2mL) was added potassium carbonate (0.216mmol,

30mg) and potassium iodide (0.02mmol, 3.2mg). The reaction was heated to 60°C before the dropwise addition of 2,4-difluorobenzyl bromide (0.196mmol, 25μL). The reaction was heated at 60°C for a further 75 minutes. Solvent was removed from the reaction and the residue partitioned between 2N HCl (1mL) and CH_2Cl_2 (2mL). The organic layer was collected and the solvent removed. The sample was purified initially by mass directed HPLC, then via an aminopropyl SPE cartridge. The desired compound was dissolved in methanol / aqueous sodium hydroxide. The organic solvent was removed under a stream of nitrogen, and the resulting suspension extracted with CH_2Cl_2. The extracts were combined, dried, and the solvent removed to yield the desired product (22.4mg, 49%). LCMS t = 3.82 min [MH^+] 440/442.

It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

ASSAYS FOR DETERMINING BIOLOGICAL ACTIVITY

The compounds of formula (I) can be tested using the following assays to demonstrate their prostanoid antagonist or agonist activity in vitro and in vivo and their selectivity. The prostaglandin receptors investigated are DP, EP_1, EP_2, EP_3, EP_4, FP, IP and TP.

The ability of compounds to antagonise EP_1 & EP_3 receptors may be demonstrated using a functional calcium mobilisation assay. Briefly, the antagonist properties of compounds are assessed by their ability to inhibit the mobilisation of intracellular calcium ($[Ca^{2+}]_i$) in response to activation of EP_1 or EP_3 receptors by the natural agonist hormone prostaglandin E_2 (PGE_2). Increasing concentrations of antagonist reduce the amount of calcium that a given concentration of PGE_2 can mobilise. The net effect is to displace the PGE_2 concentration-effect curve to higher concentrations of PGE_2. The amount of calcium produced is assessed using a calcium-sensitive fluorescent dye such as Fluo-3, AM and a suitable instrument such as a Fluorimetric Imaging Plate Reader (FLIPR). Increasing amounts of $[Ca^{2+}]_i$ produced by receptor activation increase the amount of fluorescence produced by the dye and give rise to an increasing signal. The signal may be detected using the FLIPR instrument and the data generated may be analysed with suitable curve-fitting software.

The human EP_1 or EP_3 calcium mobilisation assay (hereafter referred to as 'the calcium assay') utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing either EP_1 or EP_3 cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin and 10μg/ml puromycin.

For assay, cells are harvested using a proprietary reagent that dislodges cells such as Versene. Cells are re-suspended in a suitable quantity of fresh culture media for introduction into a 384-well plate. Following incubation for 24 hours at 37°C the culture

media is replaced with a medium containing fluo-3 and the detergent pluronic acid, and a further incubation takes place. Concentrations of compounds are then added to the plate in order to construct concentration-effect curves. This may be performed on the FLIPR in order to assess the agonist properties of the compounds. Concentrations of PGE_2 are then added to the plate in order to assess the antagonist properties of the compounds.

The data so generated may be analysed by means of a computerised curve-fitting routine. The concentration of compound that elicits a half-maximal inhibition of the calcium mobilisation induced by PGE_2 (pIC_{50}) may then be estimated.

Binding Assay for the Human Prostanoid EP_1 Receptor

Competition assay using [^{3}H]-PGE2.

Compound potencies are determined using a radioligand binding assay. In this assay compound potencies are determined from their ability to compete with tritiated prostaglandin E_2 ([^{3}H]-PGE_2) for binding to the human EP_1 receptor.

This assay utilises Chinese hamster ovary-K1 (CHO-K1) cells into which a stable vector containing the EP_1 cDNA has previously been transfected. Cells are cultured in suitable flasks containing culture medium such as DMEM:F-12 supplemented with 10% v/v foetal calf serum, 2mM L-glutamine, 0.25mg/ml geneticin, 10μg/ml puromycin and 10μM indomethacin.

Cells are detached from the culture flasks by incubation in calcium and magnesium free phosphate buffered saline containing 1 mM disodium ethylenediaminetetraacetic acid (Na_2EDTA) and 10μM indomethacin for 5 min. The cells are isolated by centrifugation at 250xg for 5mins and suspended in an ice cold buffer such as 50 mM Tris, 1mM Na_2EDTA, 140mM NaCl, 10μM indomethacin (pH 7.4). The cells are homogenised using a Polytron tissue disrupter (2x10s burst at full setting), centrifuged at 48,000xg for 20mins and the pellet containing the membrane fraction is washed three times by suspension and centrifugation at 48,000xg for 20mins. The final membrane pellet is suspended in an assay buffer such as 10mM 2-[N-morpholino]ethanesulphonic acid, 1mM Na_2EDTA, 10mM $MgCl_2$ (pH 6). Aliquots are frozen at –80°C until required.

For the binding assay the cell membranes, competing compounds and [^{3}H]-PGE_2 (3nM final assay concentration) are incubated in a final volume of 100μl for 30 min at 30°C. All reagents are prepared in assay buffer. Reactions are terminated by rapid vacuum filtration over GF/B filters using a Brandell cell harvester. The filters are washed with ice cold assay buffer, dried and the radioactivity retained on the filters is measured by liquid scintillation counting in Packard TopCount scintillation counter.

The data are analysed using non linear curve fitting techniques (GraphPad Prism 3) to determine the concentration of compound producing 50% inhibition of specific binding (IC_{50}).

By application of these techniques, compounds of the Examples had an antagonist pIC_{50} value of 6.0 to 9.0 at EP_1 receptors and pIC_{50} value of < 6.0 at EP_3 receptors.

No toxicological effects are indicated/expected when a compound (of the invention) is administered in the above mentioned dosage range.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

or bicyclic heterocyclyl group the R^1 substituent and phenyl ring are attached to substitutable carbon atoms 1,2- or 1,3- relative to each other;
and derivatives thereof.

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.